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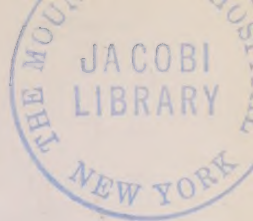
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THE CELL RESEARCH LABORATORY

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EDITOR'S NOTE

Throughout the years, The Mount Sinai Hospital has maintained a forward approach in the application of newer methods and techniques. A separate department of hematology was initiated here as early as 1923, an autonomous department of physics was founded in 1941, and one of the first psychiatric departments in a general hospital functioning in a completely integrated fashion with all other services was instituted in 1945. In keeping with this progressive tradition, one of Mount Sinai's great men, Dr. Paul Klemperer, is actively engaged in forming a new laboratory within the hospital, devoted to cell research. Under his inspiring and devoted leadership, the workers in this new laboratory will explore an imaginative new avenue in medical methodology. We are sure that our newest department will make a real contribution to our continued growth and development.

As our knowledge increases, there has been a growing conviction that a living organism is substantially more complicated than the biochemist's "bag of enzymes", and even the most elaborate of physical "machines". We now realize that hope of an *approach* to complete understanding of its behavior and function, normal and abnormal, can come only from combined structural and functional inquiries, from the organismal level down,—and from the molecular level up.

Looking up from the molecular level, the first approximately selfsufficient organismal unit that one sees which can be said to be *alive* (in the ordinary sense of the word), is the cell.

On the other hand, looking down from higher levels of organization, one finds that questions such as, "What is the mechanism of resorption in the kidney and absorption in the small intestine?"—and, "How do a hepatoma and a normal liver differ?" usually become focussed and more meaningful when recast, for example as "What is the mechanism of transport of sugar and amino acids across the free surface of the proximal tubule cell of the kidney and the columnar epithelial cell of the small intestine?"—and, "What are the differences between the hepatoma cell and the parenchyma cell of the liver?" That is to say, many of the processes of interest at the higher levels are basically *cellular* processes, and the crucial differences between normal and abnormal tissues are mainly due to the morphological and physiological differences between *specific* types of cells. Yet until 1940, our knowledge about cell structure and function was at almost as primitive a level of development as were human anatomy and physiology in Aristotle's day,—and methods for attacking these questions, especially quantitative methods, were wanting.

The cell is quite a small organism. In the human, it averages about 15 microns

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in diameter, and has a wet weight of about 4×10^{-9} grams. This puts chemical analysis of single cells a few orders of magnitude below the most sensitive micro-methods of the biochemists, and it is just this minute scale of things cellular, that had provided the block to a quantitative approach.

The chink in the cell's armor turned out to be its transparency to light,—more particularly, the fact that the degree of transparency of a cell to light of a specific wavelength is a function of the *concentration* and *kinds* of substances present in it. These can be its naturally occurring components (viz. hemoglobin of erythrocytes in the visible region of the spectrum, and nucleic acids in the ultraviolet region) or light absorbing substances added to it as a result of reactions with specific chemical reagents, or with stains. And the sword of the cytologist was nothing less prosaic than his trusty microscope,—albeit sharpened to a keener edge with added light measuring devices.

Classical cytology, like classical pathology and hematology, is a morphological science, and the law of diminishing returns had begun to take its toll as early as 1940. The idea of making spectrophotometric studies of cells in sections, smears and live tissue cultures, *through the microscope*, had sufficient heuristic appeal to revitalize this stagnating science. It gave birth to new and serious interest in the possibility of other quantitative analytical approaches to the cell's secrets involving the same high powered looking glass. The past fifteen years has seen a burgeoning of the fruits of such interest into a field which has now been dignified by its own appropriate name, Analytical Cytology. It encompasses cytochemistry; microspectrophotometry in the ultraviolet, visible, and infrared portions of the spectrum; cytological radioautography; mass determination methods by interference microscopy; fluorescence microscopy; x-ray micro-radiography; microsurgery; time-lapse microcinematography; and the recently refined morphological techniques of cytological phase and electron microscopy (1, 2).

As implied above, most biological disciplines might well profit from the "cellular approach",—but without a doubt, the cytologist's first cousins, the pathologist and hematologist have the most to gain from the new analytical cytology. It was this conviction which stimulated Paul Klemperer, in his last year as Pathologist of The Mount Sinai Hospital to suggest the creation of the Cell Research Laboratory of The Mount Sinai Hospital.

This creation went further than to merely equip and staff "another research lab". It embodies Dr. Klemperer's idea of the most profitable dove-tailing of basic research and medicine. It required a means of support of that research which would permit "freely roaming inquiries into specific areas—judged to be of significance—" with "—freedom to change the direction and emphasis of—investigation" and the possibility of "—considerable latitude in expending funds" (3). It was decided that the Cell Research Laboratory should provide an academic haven for select young pathologists and hematologists,—yet with close enough ties to the Pathology and Hematology departments to insure a healthy fusion of their medical experience and attitude with this new training and environment. The premise was that the young MD is given little opportunity to

step back long enough to gain perspective when subject to the rapid pace of medical training, the emotional pressures of medical practice, and modern society's demand for immediate "results" from medical research. It was through the continuing efforts of Dr. Richard Lewisohn that sufficient funds became available to institute the total program.

The Cell Research Laboratory is now 1 $\frac{1}{2}$ years old. It is something new at The Mount Sinai Hospital. It is also something new in postgraduate medical education. The physical plant is one of the best equipped analytical cytology laboratories in the world. Its present permanent staff consists of three non-medical biologists and one of the ablest of histological technicians. Two research fellows in hematology and pathology have begun a year's sojourn. All personnel are exposed to constant encouragement and counsel of Paul Klemperer, who, in retirement, devotes most of his time to Cell Research.

Our present research programs aim at characterizing the differences between an animal carcinoma cell and its normal counterpart as completely as possible with the battery of techniques of analytical cytology; the study in tissue culture, of the relation between the role of the different cell organelles and cellular differentiation; and the examination of the common denominator in the two kinds of anomalous growth typified by cellular hypertrophy and tissue hyperplasia. Our two fellows will be investigating an experimental animal leukemia and some of the diseases characterized by "fibrinoid".

We have attempted to indicate the origins and the hopes of this new laboratory at The Mount Sinai Hospital. If our aims are realized, this note may serve as an abridged philosophical blue-print for its duplication at other institutions.

THE RADIOGRAPHIC DIAGNOSIS OF MEDIASTINAL INVOLVEMENT IN CARCINOMA OF THE LUNG

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Carcinoma of the lung belongs to that group of malignancies which usually metastasizes early and widely. More than half of the patients are dead within one year from the time of clinical recognition of the disease despite the great strides made in the diagnosis and treatment of this neoplasm. Ineffective surgery, resulting only in the documentation of an inoperable status, is particularly undesirable in pulmonary cancer since practically no surgical palliation can be given these inoperable cases, and the short comfort and life expectancy periods of these patients may be further diminished by the operative procedure. In addition, there is the delay in beginning and the necessarily diminished dosage of palliative radiotherapy during the period of recovery from surgery. For these reasons it is highly desirable to avoid surgery in the inoperable cases.

Pulmonary carcinoma becomes categorically inoperable when it results in recognizable metastases to distant structures, involves the opposite lung or invades vital, non-resectable components of the mediastinum. It is the radiographic recognition of mediastinal invasion that is the concern of this discussion.

The mediastinum, on the routine chest roentgenogram, is a region of essentially homogeneous, water-density throughout, except for the poorly demonstrated tracheal radiolucency in its superior division. The entire area is further obscured by the denser shadow of the thoracic spine superimposed upon it in the frontal view. As a result, evidence of mediastinal invasion on the routine frontal view is restricted to lateral bulging of the mediastinal margins, and on the lateral view to mass densities in the hilar and mediastinal regions. Such findings occur in only a small proportion of those cases where actually sufficient mediastinal involvement is present to make them inoperable. Additional methods therefore have been evolved during the past decade to increase the recognition of mediastinal invasion. These techniques consist mainly in radiographically demonstrating the several tube-like structures in the mediastinum by various procedures. Evidence of displacement, compression or invasion of these visualized structures is then evaluated as possible mediastinal metastasis in cases of known carcinoma of the lung. In interpreting the findings it may be of importance to the surgeon to differentiate, if possible, between simple lymph node enlargements and actual invasion of vital mediastinal structures. The former may be technically operable, whereas invasion of vital structures makes surgical removal technically impossible and actually contra-indicates surgery. An evaluation of the desirability and success of surgery in cases with demonstrable lymph node metastases in the mediastinum, even though technically removable, is not within the scope of this presentation.

Our present roentgenologic investigation of the mediastinum for metastases in cases of cancer of the lung includes the following procedures:

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1. Fluoroscopy of the chest and larynx.
2. Routine frontal, lateral and oblique views.
3. Bucky studies of the thorax.
4. Fluoroscopic and radiographic examination of the barium-opacified esophagus.
5. Body section radiography of the chest.
6. Thoracic angiography and angiocardiography.
 - A. Innominate vein.
 - B. Superior vena cava.
 - C. Pulmonary artery and its intramediastinal right and left branches.
 - D. Azygos venous system.
7. Procedures less frequently employed requiring additional clinical evaluation.
 - A. Transverse-axial laminography.
 - B. Air-contrast mediastinography.
 - C. Opaque-contrast mediastinography.

1. *Fluoroscopy of the chest and larynx.* Fluoroscopy of the chest, with respect to mediastinal metastases, is employed primarily to determine the presence of diaphragmatic paralysis. If present, there is the implied local invasion of the phrenic nerve and middle mediastinum. In addition, there is the usual search for lateral bulges of the mediastinum and the presence of mass densities in the oblique views. These findings may furnish leads for further investigation. During the fluoroscopic examination we attempt also to visualize the larynx in the frontal view while the patient says "e". In a number of instances we have thereby called attention to a paralyzed hemilarynx, indicative of recurrent laryngeal paralysis and an inoperable status of the pulmonary carcinoma.

2. *Routine frontal, lateral and oblique views.* These are, of course, a necessity in the study of the mediastinum as well as the lungs. The findings to be sought are too well known to require any discussion, except to indicate that the location of suspicious findings often gives direction to the exploration by more detailed techniques.

3. *Bucky Studies of the Thorax.* These are employed for information concerning the dorsal spine, which forms the posterior boundary of the mediastinum. In addition, the marked density and contrast of the film permit better visualization of the trachea and main bronchi than on the routine studies. However, these important structures are studied even more satisfactorily by body section radiography.

4. *Fluoroscopic and radiographic examination of the barium-opacified esophagus (1, 2).* This method represents one of the keystones of the mediastinal study. The esophagus, as it descends, lies posterior to and in intimate contact with aorta, the trachea, the interbronchial area and the left auricle. In the interbronchial zone, it is situated just behind and near both hilar regions. Lymph node enlargements or actual mediastinal invasions adjacent the esophagus may simply displace the esophagus, compress it or actually invade its wall. Any one or a combination of findings may be encountered. Simple displacements and

compression are easily determined. Evaluation for wall invasion requires study of the esophageal mucosal pattern. Local narrowing of the esophageal lumen with flattening, semilunar distortion and angulation of mucosal pattern are typical of the intramural extramucosal lesion and indicate wall involvement. More advanced invasion is shown by actual local destruction of the mucosal pattern, the appearance of an ulcer niche in the involved zone and, finally, the formation of a carcinomatous fistulous tract into the mediastinum itself or the adjacent trachea. The interbronchial zone, immediately below the tracheal bifurcation and between the main bronchi, is one of the most frequent sites of lymph node metastases from pulmonary carcinoma. The esophagus, lying in immediate apposition to the interbronchial area, is an excellent indicator of metastasis in this region. Localized, posterior displacement, compression and or invasion of the esophagus just below the tracheal bifurcation and above the normal left auricular impression are searched for in each case with particular care. The width of the space between the opacified esophagus and the trachea in the lateral view is also routinely noted. Enlarged nodes or masses adjacent the trachea not infrequently cause local widening of this space. In some instances the posterior displacement of the esophagus may be used to evaluate the effectiveness of radiotherapy. As the mediastinal masses diminish, the esophagus assumes a normal course and the displacement disappears (Fig. 1).

5. *Body section roentgenography* is an essential part of the mediastinal study. In studying the mediastinum by this method it is necessary to employ 2 to 2½ times the exposure used for the routine chest sections. These additional films, usually at the 8, 9, and 10 cm. levels, are added to the routine thoracic tomograms of the parenchymal lesion. A clear demonstration of the air-filled,

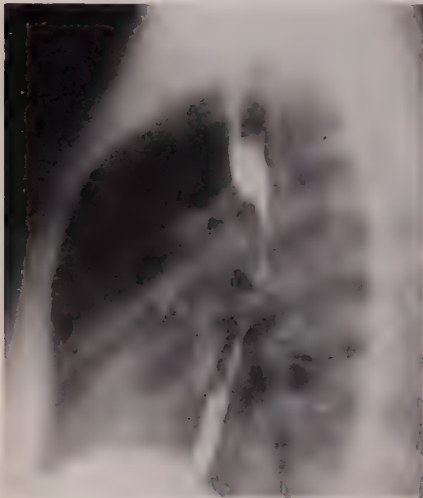


FIG. 1a

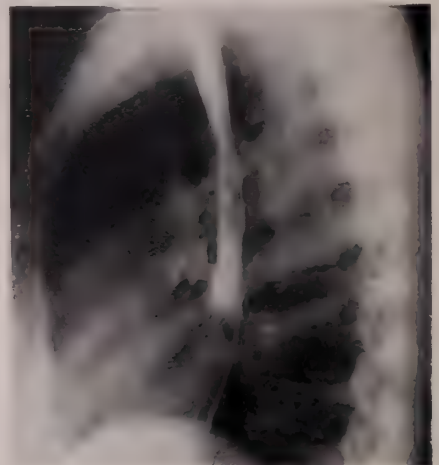


FIG. 1b

FIG. 1a. Marked local compression and displacement of the midesophagus by enlarged interbronchial angle nodes from proven squamous cell carcinoma of lung.

FIG. 1b. Same case following supervoltage radiotherapy. Compression and displacement have disappeared.

radiolucent trachea and main bronchi lying within the mediastinal shadow is obtained. A number of manifestations of mediastinal involvement may be elicited from this study. Enlarged paratracheal, tracheobronchial or interbronchial lymph nodes can be demonstrated by their production of local, semilunar indentations in the lumina of the trachea or bronchi (Fig. 2). Larger masses cause correspondingly greater semilunar indentations in the lumina and actual compression, distortion or displacement of the trachea and bronchi (Fig. 3). A finding frequently associated with enlarged interbronchial nodes is actual widening of the interbronchial angle, just distal to the tracheal bifurcation. This widening is usually accompanied by lobular indentations in the bronchial walls made by the nodes. Any evidence of extrinsic pressure upon the tracheal lumen or in the region of the bifurcation may be assumed to be due to involvement within the mediastinum. However, the site of pressure on the main bronchi must be carefully evaluated with respect to its location in or out of the mediastinum. Only lesions less than 1.5 to 2.0 cm. from the tracheal bifurcation can be considered as being within the mediastinal area. Very often, body section roentgenograms will demonstrate pressure effects on the bronchi distal to these points. These findings result from lymph node enlargements or the primary lesion itself in the hilar region or pulmonary



FIG. 2. Angulation of the right tracheobronchial angle and irregular, small semilunar indentations on right main bronchus by a proven, inoperable large mediastinal mass.

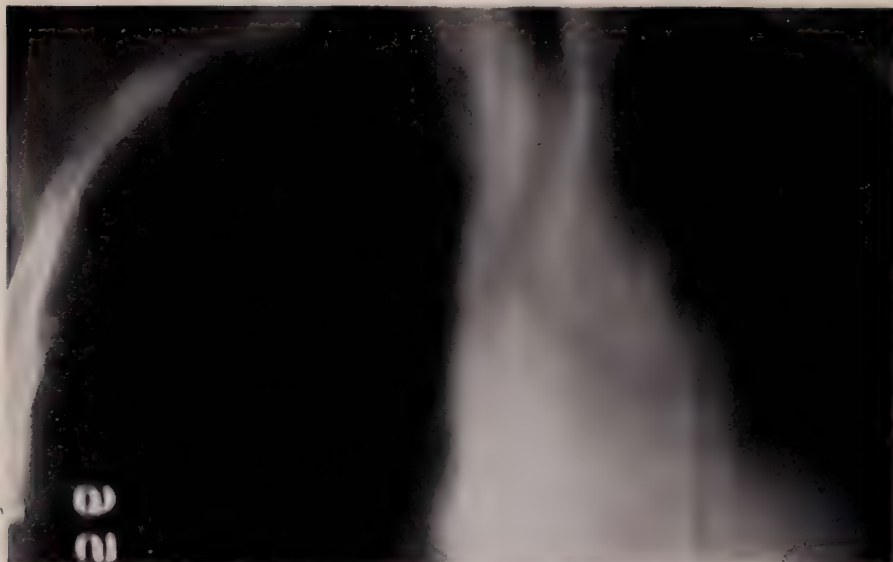


FIG. 3. Narrowing and displacement of trachea and left main bronchus by greatly enlarged left tracheobronchial nodes. Operative proof.

parenchyma medially. While they aid in demonstrating the site of involvement, they do not indicate inoperability.

Marked irregularity of the margin of the narrowed tracheal or bronchial airway is indicative of actual involvement of its wall. When the local narrowing is angular or polypoid, invasion of the wall is almost certain.

Body section roentgenography is also of great aid in determining mediastinal extension in cases with juxta-hilar, medial or para-mediastinal primary parenchymal tumors. Where direct extension from the lung into the mediastinum has occurred, a single homogeneous mass-density can be demonstrated extending from the lung into the mediastinum at the appropriate tomographic level. This continuous homogeneous opacity involving the medial lung field and adjacent mediastinum has been found constantly to indicate inoperable extension into the mediastinum. Cases without mediastinal involvement have shown a comparatively radiolucent zone of varying width between the pulmonary tumor and the mediastinum.

6. *Thoracic angiography and angiocardigraphy* (3, 4, 5). This technique has become a routine component of the mediastinal study. Usually, 50 ml. of one of the high-iodine-content contrast materials are rapidly injected. The injection is made into the antecubital vein on the side of the neoplasm. We have employed a Fairchild rapid film changer and taken radiographs at 1 second intervals for up to 20 seconds, but such devices, although desirable, are not necessary for adequate studies.

The primary areas of interest in these studies are, of course, not the heart, but rather the major vessels in the mediastinum. These are principally the innominate vein, the superior vena cava, the pulmonary artery and its two

major branches within the mediastinum. We have noted three types of alteration in the appearance of these vessels due to mediastinal involvement. The first of these is simple compression and or displacement of the vessel by an extrinsic mass not necessarily adherent to the vessel wall, usually an enlarged lymph node. The indentation in the vessel is smooth, regular and comparatively broad. Nodes or masses causing such appearances are still theoretically resectable.

The second is complete obstruction of a vessel. Complete occlusion of the innominate vein or superior vena cava by neoplasm has always been found associated with extensive collateral circulation of the usual bizarre patterns (Fig. 4). Indeed, the absence of such collateralization makes the diagnosis of complete venous obstruction doubtful. These cases are frequently found to have superior mediastinal obstruction syndromes. We have not encountered a documented case with such vascular obstruction which was even technically operable, and believe that the finding of complete venous obstruction of the innominate vein or superior vena cava indicates technical inoperability when associated with carcinoma of the lung.

Complete obstruction of the right or left major pulmonary arteries on the same side as the carcinoma has been encountered in a number of patients. The findings have usually been recorded on films made between 4 and 9 seconds after injection of the contrast material. Occlusion is evidenced by an abrupt, complete interruption of the opacified vessel (Fig. 5). It is essential that adequate visualization of the pulmonary vessels be obtained in order to prevent simulation of obstruction by incomplete filling with contrast material. A satisfactory test of filling is usually the opposite, uninvolved pulmonary artery. If the latter is well filled and normal appearing, the interrupted pattern on the involved side may



FIG. 4a

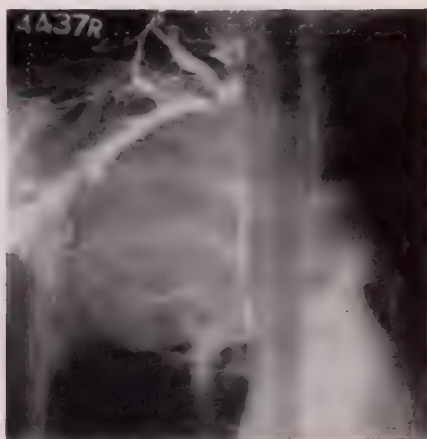


FIG. 4b

FIG. 4a. Complete obstruction left innominate vein and superior vena cava by mediastinal invasion of pulmonary carcinoma. Extensive collateralization, including azygos system.

FIG. 4b. Complete obstruction right innominate vein. Extensive collateralization, including internal mammary vein.

safely be interpreted as due to occlusion. Care in interpretation is essential with the pulmonary artery obstructions since these are not accompanied by radiographically demonstrable collateral circulation such as is seen with the venous occlusions. The site of the obstruction in the pulmonary artery is of great importance in determining the location of involvement in the mediastinum and the operability of the case. Complete occlusions of the branches of the pulmonary arteries in the parenchyma near the primary tumors are comparatively common and do not contra-indicate surgery. To be considered as indicative of mediastinal invasion, the obstruction must occur within the mediastinal shadow. On the left side, the pulmonary artery block must be within 1.0 to 1.5 cm. from the bifurcation. Obstructions distal to these points are not considered as mediastinal and do not of themselves contra-indicate surgical approach. All bifurcations of the right and left main pulmonary arteries occur outside of the mediastinum. In the cases where the obstructions occurred within the mediastinum and the patients were explored, there were no instances where resection could have been attempted and all these patients were considered technically inoperable. At present, we therefore consider intra-mediastinal pulmonary artery obstruction as evidence of technical inoperability.

In addition to simple displacement, smooth semilunar compression and complete obstruction, the various opacified major mediastinal vessels may show local mottling of their shadows. This appearance is characterized by multiple irregular, nodular, ovoid and streak-like filling defects within the local segment of the opacified vessel (Fig. 6). Usually, the involved lumen shows some narrowing as well, although actual widening by intraluminal masses is occasionally seen. These findings are indicative of actual invasion of the wall and lumen of the involved vessel, which in turn implies invasion of the mediastinum and in-



FIG. 5

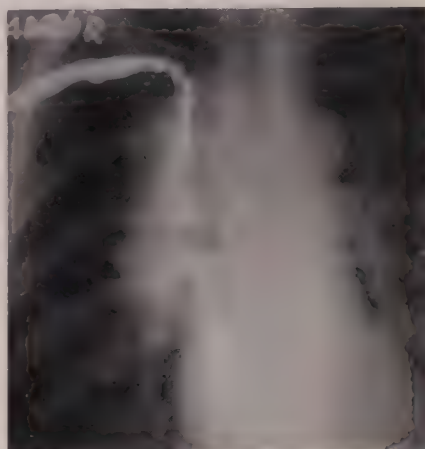


FIG. 6

FIG. 5. Complete obstruction right main pulmonary artery by proven mediastinal metastases from carcinoma of lung. Left pulmonary artery normal.

FIG. 6. Wall and lumen invasion of superior vena cava by proven mediastinal metastases. Note irregular small and large mottled filling defects in the opacified column. Vascular channels proximal and distal to involved area are well filled.

operability. Adequate filling of the vessel proximal and distal to the area of mottling is essential to the diagnosis since incomplete filling with the contrast material may simulate such defects to a considerable degree. With increasing obstruction of the veins by the intraluminal growths collateralization occurs and serves to corroborate the diagnosis.

Significant involvement of the posterior mediastinum may be shown by demonstrating alterations or obstruction in the azygos or hemiazygos veins (6, 7). The azygos vein proceeds upward in the right posterior mediastinum and enters the superior vena cava. Involvement of this region could therefore be demonstrated by changes in the azygos vein similar to those described above for the other mediastinal veins. The findings with complete obstruction are somewhat variable however. We have observed that collateralization may not be significantly greater than is seen normally. On the other hand, opacification of the azygos vein ends abruptly well below its entrance into the superior vena cava. Instead, the opacification of the vein is seen to proceed downward into the abdomen, indicating a reversal of direction of the blood flow in this vessel. Demonstrating this channel may also be helpful in cases of obstruction of the subclavian and innominate veins. In these latter instances it may be of value to know if the superior vena cava is patent or also occluded. If injection of the azygos vein results in visualization to the superior vena cava, the latter's patency may be presumed.

Visualization of the azygos vein on the right side, or hemiazygos vein on the left side, is obtained by placing a marrow aspiration needle into the cancellous center of one of the lower ribs posteriorly. Ten to 15 ml. of high-iodine-concentration contrast material are injected as rapidly as possible, and the first film is made at the end of the injection. The injection usually requires between 5 and 10 seconds. At the conclusion of this period, much of the contrast material has left the cancellous space, opacified the intercostal veins, entered and visualized the azygous vein and reached the superior vena cava (Fig. 7). The posterior medias-



FIG. 7. Opacification of azygos vein following injection of contrast material into right 9th rib posteriorly. The vein is displaced to left, but of normal calibre.

tinum adjacent the azygos system is involved by carcinoma of the lung infrequently, and we feel that this procedure should not be adopted as a routine, as in esophageal carcinoma, but rather reserved for the indicated occasions.

7. *Infrequently employed procedures*—such as transverse-axial laminography (8), air contrast mediastinography, opaque contrast mediastinography (9) and combined air contrast visualization of the mediastinum with transverse-axial laminography (10) have been reported occasionally during the past five years. Transverse-axial laminography is as the name indicates, an obliquely vertical body section roentgenography which results in radiographs resembling cross-sectional “cuts” through the chest and mediastinum. It is not in common use, and its greatest value at present appears to be in the antero-posterior localization of tumors in the mediastinum rather than the demonstration of a mediastinal tumor not recognized by other radiographic techniques. Air contrast mediastinography has been employed frequently in infants and children for the better elucidation of anterior mediastinal masses, particularly enlarged thymuses. Varying amounts of air or carbon dioxide, up to 30 ml., are injected percutaneously through a needle placed just behind the sternum. The gas diffuses throughout the mediastinum and may improve visualization of masses in this region. The thymus outline may be thus better delineated than on the routine studies. Air contrast mediastinography and transverse-axial laminography can be combined to advantage for the antero-posterior localization of mediastinal masses on the cross-sectional films. These methods have as yet not been adequately explored in the investigation of mediastinal metastases, and their status and importance are thus not established. However, the preliminary results are sufficiently promising to warrant further study.

Opaque contrast mediastinography involves the percutaneous injection of 50–100 ml. of one of the highly iodinated contrast substances into the mediastinum, followed by routine radiographic studies. The method is still experimental, and little can be said concerning any usefulness as yet.

SUMMARY

Since cases with inoperable cancer of the lung have a short life expectancy and since no significant palliation can be offered these unfortunate patients by surgery, all available procedures should be employed to avoid unnecessary surgery for these inoperable lesions. A battery of radiographic examinations has been evolved which has greatly increased the accuracy and frequency of the diagnosis of mediastinal invasion. These procedures include fluoroscopy, routine radiography in the various obliques, Bucky examinations, esophagrams, body section roentgenography, thoracic angiograms of several types and contrast mediastinography.

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A PHYSIOLOGICAL EVALUATION OF PSYCHIATRIC PATIENTS*

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INTRODUCTION AND BACKGROUND

Cannon's classical studies have provided the greatest impetus for modern experimental psychological research. He described emergency behavior in animals from a psychological and physiological standpoint. On the psychological level he described his findings in terms of the fight-flight reaction, and on the physical level showed that the changes during the reaction involved over-secretion of epinephrine. As a logical outgrowth of these and other allied studies, psychological experimental research has divided into two pathways. One approach has been the attempt to modify abnormal emotional states by the administration of drugs affecting the autonomic system, i.e., reserpine and chlorpromazine. The other pathway has been through the use of the newer and more refined biochemical and neurophysiological techniques of investigation, the latter in an effort to gain a more comprehensive understanding of the interplay of the psyche and soma both in health and disease.

This paper is a preliminary report on the use of the Funkenstein Test (1-8), as a physiological adjuvant, to help in the evaluation and treatment of psychiatric patients. This test was administered to 53 patients admitted to The Mount Sinai Hospital Psychiatric Service from September, 1955 to March, 1956. These patients have been studied serially, from the psychological and physiological points of view. Although concerned with the same organism, the psychiatrist and the physiologist use different methods of examination and different frames of reference. In our study we attempted to combine these two approaches: on the one hand utilizing the "communicated introspection" of the psychiatrist; on the other hand utilizing the Funkenstein Test as a sensitive indicator of autonomic nervous system responsivity.

The Funkenstein Test utilizes the intravenous administration of adrenalin (0.025 mg.) and the intramuscular administration of mecholyl (10 mg.) to measure the autonomic balance of the patient. In addition we have employed nor-adrenalin as a testing agent. On the basis of the degree and duration of the hypertensive and hypotensive effects of these drugs, Funkenstein divided the patients into seven distinct groups (Chart I):

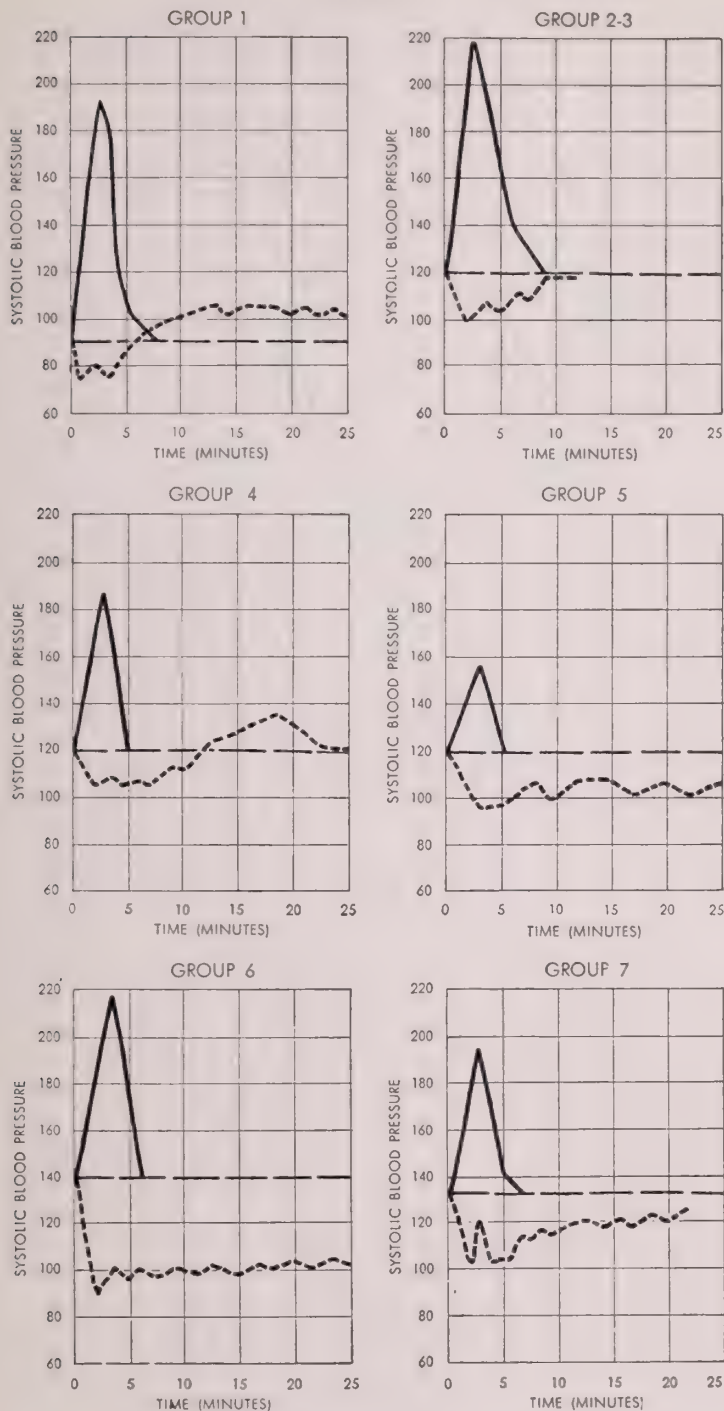
Group I: Epinephrine—rise in systolic blood pressure in excess of 50 mm. Hg. Mecholyl—slight fall in systolic blood pressure with early rise above pre-injection level and failure to return to the pre-injection level during the twenty-five minute observation period.

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* Presented at the Combined Conference of the Psychiatry & Neurology Departments, The Mount Sinai Hospital, April 3, 1956.

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CHART I



Groups II and III: Epinephrine—rise in systolic blood pressure in excess of 50 mm. Hg. Mecholyl—moderate or slight fall in systolic blood pressure with or without slight rise above pre-injection level but with establishment of homeostasis, i.e., return to pre-injection level of blood pressure and maintenance of it, within the twenty-five minute observation period.

Group IV: Epinephrine—rise in systolic blood pressure in excess of 50 mm. Hg. Mecholyl—moderate fall in systolic blood pressure with marked compensatory delayed rise before establishment of homeostasis (return to pre-injection level and maintenance of it for three to five minutes within the twenty-five minute observation period).

Group V: Epinephrine—rise in systolic blood pressure of 50 mm. Hg or less. Mecholyl—fall in systolic blood pressure with failure to reach pre-injection blood pressure level within the twenty-five minute observation period.

Group VI: Epinephrine—rise in systolic blood pressure in excess of 50 mm. Hg. Mecholyl—fall in systolic blood pressure with failure to reach pre-injection blood pressure level within the twenty-five minute observation period.

Group VII: In this group are included all cases in which a "chill" occurred after mecholyl. A reliable blood pressure curve could not be obtained because of noise engendered by the muscular contractures during the chill.

Groups I and IV are therefore characterized by a hyperreactivity of sympathetico-adrenal discharges in response to mecholyl; Groups V, VI, and VII show a hyporeactivity of this system, and Groups II and III normal sympathetic reaction.

Funkenstein made the fundamental clinical observation that the favorable response to electroshock therapy is linked with certain autonomic groupings; namely Groups VI and VII where there is a prolonged hypotensive response to mecholyl indicating a hyporeactivity of the sympathetic centers. He found that this autonomic pattern was more reliable in making a prognosis for electroshock response than the diagnostic classification based on clinical symptoms. He also found that in successful therapy the altered mental state was associated with a change in reaction to mecholyl, i.e., from Group VI or VII to Group II or III. Therefore he concluded that "... when the psychological picture changes the physiological picture changes and vice versa." That is, improvement of the clinical condition of the patient is associated with an alteration in the blood pressure reactions that are induced by mecholyl and adrenalin. If these reactions do not change, then the clinical picture is unaltered.

An obvious factor which merits consideration in research on psychophysiological responsiveness is the level of physiological activity which is being tapped by the particular measures employed. It is beyond the scope of this paper to present all the experimental data that validate the relationship between the injection of peripherally acting drugs such as mecholyl and adrenalin and the fact that it is the central nervous system hypothalamic structures that determine the resultant blood pressure effects. Numerous experimental studies, utilizing hypophysectomized animals, autonomic blocking agents and denervated peripheral preparations have shown that the degree and duration of the hypotensive effect of

mecholy) are inversely related to the degree of sympathetico-adrenal discharges; that parasympathetic discharges play no role; and that it is the central nervous system structures that determine the resultant blood pressure effects.

Our purpose in initiating this investigation was threefold:

1. To determine whether the Funkenstein Test could be used to predict those cases that would respond favorably to reserpine and chlorpromazine. As mentioned previously, this Test has been utilized successfully to predict those cases that would respond favorably to electroshock therapy. In particular we wanted to know whether the symptomatic changes following the use of the tranquilizing drugs are accompanied by changes in the autonomic balance.

2. To investigate the possibility of a correlation, causal or incidental, between the psychosomatic manifestations of our patient and their autonomic balance, as determined by the Funkenstein Test.

3. To investigate the possibility of any autonomic shift in those patients who might demonstrate the so-called alternation of physical disease and its emotional equivalent, i.e., asthma and depression, ulcerative colitis and psychosis.

METHOD

Fifty-three patients from The Mount Sinai Hospital Psychiatric Service, New York, form the basis for this study. They were unselected and consecutive admissions (with the exception of severe asthmatics and patients with extensive cardiovascular involvement).

Each patient under basal conditions remains in bed for at least 20 minutes. Systolic blood pressure determinations are made by the cuff and stethoscope method every three minutes. After a basal systolic reading has been determined, the patient receives 1 cc. of isotonic saline solution intravenously. Then the systolic blood pressure is followed every minute for 10 minutes. On the next day, the patient receives 0.025 mg. of epinephrine intravenously and the systolic blood pressure is followed at intervals of one minute until it returns to the basal level. On the third day, under similar basal conditions, the patient receives 10 mg. of mecholy) subcutaneously, and the systolic blood pressure is followed for twenty-five minutes. During the administration of each drug, it is also noted whether the patient shows pallor, anxiety, flush, sweating or a shaking chill. The graphs are obtained by superimposing the systolic blood pressure responses to mecholy) and adrenalin on the same graph (although the readings are obtained on different days).

For the purpose of this preliminary report, the case material was analyzed from the following point of view:

1. The varieties of subjective and objective distress or relief which might occur after the administration of adrenalin, noradrenalin and mecholy).

2. Any shifts in the autonomic grouping prior, during and subsequent to the various therapies (which in our series included hospitalization and observation only, superficial and intensive psychotherapy, electroshock therapy, and tranquilizing drug therapy).

Before presenting our findings, I would like to emphasize one additional

relationship that must be kept in mind when evaluating drug therapy or drug investigation; namely, the drug specific and personality specific response. By drug specific response we mean everyone will react with certain predictable responses within a given range to a specific drug. By personality specific response we mean a given personality always reacts to a drug more or less in the same way. As an example, human studies with the hallucinogenic drugs mescaline and L.S.D., which are marked equilibrium-disturbing stimuli, demonstrate that it is the personality specific reaction that is more important than the drug specific reaction. Healthy medical students regard this experience as ego-alien, respond with minimal anxiety, throw up little defenses and maintain their ego integration. When compared with subjects who experience frightening or gratifying hallucinations, depersonalization and other severe regressive phenomena, one is impressed with the importance of the prior ego integration and prior defensive mechanisms utilized in evaluating drug therapy.

In all of our subjects certain constant physiological phenomena were elicited in response to the injection of adrenalin, mechloral and noradrenalin. The injection of adrenalin was followed in all cases by increased blood pressure and systolic rate and subjectively by heart palpitations and tremors. The injection of mechloral was followed in all cases by lowering of the blood pressure, salivation, profuse sweating and flushing of the face. The injection of noradrenalin was followed in all cases by an increase in the blood pressure, heart pounding and pressure in the head. The quantitative physiological variability was great from patient to patient in response to the injection of equivalent amounts of the drug.

These physiological manifestations had no relationship whatsoever to the specific emotional reaction subjectively perceived, i.e., two patients would respond to the injection of mechloral with a physiologically identical response, however one patient would experience no anxiety while the other patient would go into an acute depersonalization reaction. As another illustration, an injection of adrenalin would create marked anxiety in a patient who exhibited minimal physiological reaction to the drug, while another patient would exhibit minimal anxiety to a severe physiological reaction to the drug. Any of these drugs could precipitate a severe anxiety attack. Mechloral, however, in over forty per cent of our patients had a euphoric, relaxant or relieving effect on the patient. This relaxant or tranquillizing effect never occurred with adrenalin or noradrenalin.

The next set of data concerns the various shifts in autonomic balance following the various therapies. Our working hypothesis was that all forms of therapy produce a psychological and physiological disturbance on the organism, to which the patient reacts to regain a new homeostasis. Our therapy is of course oriented around the possibility that the new equilibrium is less dominated by emotional factors.

The initial testings, on admission, disclosed the following distribution of autonomic groupings (Chart II):

Several conclusions are suggested from this type of breakdown of our patients into their autonomic groupings:

1. There is a definite clustering of agitated depressions, involutional depressions, schizo-affective reactions, and reactive depressions in the cholinergic

CHART II

Group I	Group II, III	Group IV	Group V	Group VI	Group VII
Ulcerative colitis (schizophrenia)	Peptic Ulcer (depression)	Alcoholism (person. disorder)	Neurocirculatory asthenia	Involutional depression	Post-partum psychosis
Sprue (obs. compulsive)	Alcoholism (person. disorder)	Anorexia nervosa (hyster. person.)	Hypochondriasis	Involutional depression	Post-partum psychosis
Schizophrenia (paranoid type)	Schizophrenia (mixed)	Conversion hysteria	Hypochondriasis	Reactive depression	
Diabetes (anxiety reaction)		Schizophrenia (somatization)	Involutional depression	Involutional depression	
Ulcerative colitis (obs. compulsive)		Schizophrenia (somatization)	Reactive depression	Schizo-affective reaction (depression)	
Schizophrenia (homosexual panic)		Hypertension (character disorder)	Schizophrenia (hypochondriasis depression)	Manic-depressive reaction	
Anorexia nervosa (hysterical person.)		Conversion hysteria		Involutional depression	
Regional ileitis (obs. compulsive)		Anxiety reaction		Reactive depression	
				Psychotic depression	
Ulcerative colitis (schizophrenia)		Lupus erythematosus (reactive depression)		Phobic reaction (depression)	
Neurodermatitis (hysterical person.)		Ulcerative colitis (obs. compulsive)		Senile psychosis (depression)	
Ulcerative colitis (obs. compulsive)		Schizophrenic reaction (mixed)		Catatonic stupor	
Ulcerative colitis				Schizoaffective reaction	
Ulcerative colitis				Manic-depressive reaction	
Parkinsonism (anxiety reaction)				Schizophrenia (depression)	
				Involutional Depression	
				Schizophrenia (depression)	

Groups V, VI and VII. The so-called psychosomatic illnesses and somatization reactions show a definite clustering in the adrenergic Groups I and IV.

2. The clinical grouping of schizophrenic reaction falls into every autonomic group with some preponderance for Groups I, IV and VI.

3. Most of our active psychosomatic cases (from the point of view of physical symptomatology) showed evidence of increased adrenergic balance and fell into Groups I and IV. We have had five cases in which the active somatic illness was replaced by a depression or emotional dysregulation (the so-called alternation of symptoms). These alternations took place spontaneously, as a result of psychotherapy, or as a result of chemotherapy principally with the tranquillizing drugs. When these patients were in the midst of a depressive reaction, they were asymptomatic in regard to their physical symptomatology. On the Funkenstein Test they had shifted autonomic groupings from their initial Group I or IV reactive pattern to V, VI, or VII reactive pattern. *Recent experimental evidence indicates that this is not a shift from adrenergic to cholinergic hyperactivity, but is a shift from noradrenalin to adrenalin hyperactivity.* As the depression began to lift, the active somatic symptomatology began to return. Coincident with the return of their initial symptoms was the return of their initial autonomic reactive patterns. Thus the effect of the autonomic balance on the personality, and the effects of the personality and stress on the autonomic balance must be taken into consideration. The autonomic endowment may be looked upon as one factor which predisposes the individual to somatic changes and to specific psychosomatic disease.

4. The relatively few patients studied permit only a superficial discussion of the relationship of the tranquillizing drugs, psychosomatic manifestations and autonomic balance. There does appear to be more involved, however, than just symptomatic changes in response to reserpine and chlorpromazine. When these drugs are given and there is a change in the patients' clinical symptomatology, there is always a shift in autonomic balance. There is no such autonomic shift, despite changes in the clinical symptomatology, following Miltown, barbiturates and meratran. This Test has not proved successful in affording us a scientific basis for predicting those patients who would respond favorably to chlorpromazine and reserpine.

5. Seven patients in this series fell into favorable autonomic groupings in regard to prognosis for electroshock therapy. They responded to electroshock with favorable clinical and autonomic changes. Three patients were given electroshock who did not fall into the favorable autonomic groupings. They did not shift autonomic groupings, nor did they show any clinical improvement.

SUMMARY AND CONCLUSIONS

It is of course very easy to sprout big theories from little data, in our case only fifty-three patients. There has been no thought on our part that the personality is being "laid bare" through these drugs and autonomic patterns. We feel we are getting another view of the personality, quite analogous to the different layers examined by the stethoscope, fluoroscope and x-ray. Different elements of the

picture are seen with greater or lesser clarity depending on the modality of investigation. It has taken us a long time to free ourselves of the obligation to classify an illness as either "psychic or physical". It is now recognized that these terms characterize not the disease, but the methods of the investigator. Every illness must be explored by both psychological and physiological tools and the findings synchronized and cross-interpreted. Only then can we say that we are practicing holistic medicine.

Our present feelings about the questions that initially stimulated this investigation can be summarized as follows:

1. There appears to be a relationship between the physical manifestations of psychosomatic illness and the psychological manifestations of psychosomatic illness. This relationship is not only from a phenomenological point of view, but from an autonomic point of view.

2. The specific response of anxiety to the administration of the testing drugs and their various inter-relationships appears to offer a particularly fruitful area of investigation in regard to extending our present-day concepts of anxiety.

3. Our results appear to provide further evidence for the psychophysiological unity of the organism in the sense that even the finest nuances of psychological events may be found to have a corresponding differentiation on the physiological level.

The questions that appear to be raised from a study of this nature are:

1. Are there patterns of physiological reaction which may be diagnostic of the primary emotional states?

2. Can the physiological reactions serve as an emotional or motivational indicator during psychological observation?

3. Are fear and anger essentially similar physiological reactions as Cannon hypothesized?

If we can find the answers to these questions, then one of Freud's most provocative speculations might come closer to realization. He always postulated that human drives or instincts are based on somatic and mental properties, and that human behavior is influenced by interacting circumstances in these two areas. He prophesied that it would be possible, someday, to influence mental life by the administration of substances of bodily organs.

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ABOLITION OF MASS FEMORAL MUSCULAR CONTRACTIONS DURING TRANSURETHRAL RESECTION

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One of the many hazards of transurethral resective procedures is the occurrence of mass muscular contractions of the lower extremities in the midst of the manipulations. The muscular reactions are apparently caused by stimulation of adjacent large nerves by high frequency electric current transmitted through the intact bladder wall from the resectoscope loop. As a product of the ensuing muscular contractions of the lower extremities, there is a resultant violent movement of the pelvis and lower trunk, and a sudden shifting of the distended bladder against the rigid sheath of the instrument. It is thus fairly easy to produce a traumatic perforation of the bladder with all the ensuing difficulties associated with this catastrophe.

The reaction seems to consist mainly of adductive movements of the medial thigh muscles. These muscles, the gracilis, the adductor group, the pectineus, and obturator externus have motor innervation from the obturator nerve. The obturator nerve bears a close anatomical relationship to the ureter, distended bladder and prostatic urethra. In addition, this muscular reflex is most often seen when lesions in the inferolateral areas of the bladder (inferior and lateral to the ureteral orifices) adjacent to the internal sphincter are being electro-resected or electrocoagulated. It is in these anatomical areas that the distended bladder is closest to the obturator nerve and the muscular reflex is most easily obtained. Actually, this annoying complication occurs infrequently during routine transurethral prostatic resection, although it occasionally occurs when the inferolateral capsule between 4 and 8 o'clock at the internal sphincter has been exposed. It most often occurs when sessile infiltrating tumors in the described areas are being resected and fulgurated and the bases are being exposed. It is at this critical time when thorough resection and coagulation into the bladder musculature has to be done if a cure is to be hoped for that the annoying and sometimes disastrous muscular reflex occurs.

It is a little odd that this particular complication is not mentioned in the texts and papers on transurethral resection. Surely it occurs not infrequently and has been a subject of discussion among the urologists and anesthetists at our institution. Various suggestions were made towards a solution of this problem, but heretofore no successful or practical schemes were devised. Cutting down the strength of the cutting current, larger initial doses of spinal anesthesia, simultaneous administration of spinal and pentothal anesthetics were ineffectual. Separate sciatic block was suggested, but since this in itself is a rather formidable

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procedure, and since most of the reaction is apparently from obturator nerve stimulation it did not seem reasonable to attempt this procedure. While the Wappler electrical generator (Radio tube high frequency current) is almost exclusively used for transurethral resection at this hospital, occasionally the Bovie generator (Spark-gap high frequency current) is used. The mass muscular contractions described have been seen with the use of either generator.

Spinal anesthesia is used with rare exception for transurethral resection. The fact that mass muscular responses are not obviated after administration of this anesthesia is interesting. However, it must be remembered that intrathecal injection of an anesthetic agent produces sensory anesthesia at the dorsal root ganglion and motor anesthesia at the ventral root. In this way practically all of the spinal reflexes are abolished. However, the peripheral mixed nerve distal to the roots maintains its integrity, and can respond to direct electrical stimulation. The necessity to block the striated myoneural junction thus becomes obvious, and the decision was made to use curare in the form of d-tubo curarine administered intravenously. This drug is believed to have its effect by its interference with the activity of acetylcholine at the myoneural junction thus abolishing the transmission of the nervous impulses to muscle.

Recently, during the resection and electrocoagulation of a malignant papillomatous tumor of the bladder situated just below and lateral to the right ureteral orifice, each time the coagulation current was applied to the base of the tumor, the papillomatous mass having previously been resected without event, there was mass adductor femoral response with ensuing violent movements of the trunk, so that the operator despaired of destroying the obviously viable tissue still remaining. At this point 3 mgm. of d-tubo curarine was administered intravenously. In a few minutes there appeared an obvious weakness of the upper extremities and some lid lag. There was apparently no interference with respiratory musculature and movements of the thoracic cage were closely observed. At the end of 5 minutes the operator resumed deep coagulation of the base of the tumor. There was a complete abolition of obturator response and the procedure was completed quickly and thoroughly.

Since that time additional cases have been done in which the use of a myoneural blocking agent was deemed necessary. A brief summary of each case will be appended. In general, the following technic and criteria have been applied. The spinal anesthetic in each case was pontocaine 12-14 mgm. in a hyperbaric glucose solution. The procedure contemplated, either transurethral prostatic resection or transurethral resection of a bladder tumor was commenced. If no untoward muscular reaction was obtained the procedure was carried to completion. If mass muscular reaction occurred, several repeated stimuli were given to be sure that the reaction was constant. If this was the case, d-tubo curarine was administered intravenously. In all of the cases 3.0 mgm. were given. One case required the administration of an additional 3.0 mgm. within 10 minutes after the administration of the initial dose. In each case, the adductor femoral contractions were abolished. The doses of d-tubo curarine are quite small compared to the amount necessary for muscular relaxation when general anesthesia

is used. However, each time significant pharmacological effects were noted in the form of upper extremity weakness, lid lag, and the abolition of femoral adductor muscular response.

Additional interesting pharmacologic and neurologic observations arising from these studies will be pursued and reported upon at a later date. The use of succinyl-choline in a regulated intravenous drip is also being evaluated.

BRIEF REVIEW OF CASES

1. Transurethral resection of infiltrating transitional cell carcinoma of the bladder located just inferolateral to the right ureter orifice. Mass adductor reflex obtained while fulgurating the base of the tumor. Reflexes abolished by the intravenous administration of 3.0 mgm. of d-tubo curarine.

2. Transurethral resection of benign papillary tumor of the bladder situated inferolateral to the left ureter orifice and extending down into the left lateral intra-urethral prostatic urethra. Adductor reflex obtained while resecting the main mass of the tumor. Reflexes abolished after intravenous administration of 6.0 mgm. of d-tubo curarine given in 3.0 mgm. increments 10 minutes apart.

3. Transurethral prostatic resection—6 cases. Adductor reflexes of annoying intensity and frequency occurring during resection of lateral intra-urethral prostatic masses upon approaching the capsular areas. Reflexes abolished in each case by the intravenous administration of 3.0 mgm. of d-tubo curarine.

SUMMARY AND CONCLUSIONS

1. D-tubo curarine in small (3–6 mgm.) doses administered intravenously has been used to abolish femoral adductor muscular responses during transurethral resection.

2. It is postulated that these muscular responses are mediated through an intact mixed peripheral nerve which can transmit electrical responses to the myoneural junction even after the spinal reflexes have been blocked by intrathecal administration of a spinal anesthetic. The nerve involved is most likely the obturator which is in anatomical proximity to the ureter, the lower bladder wall and wall of the prostatic urethra. D-tubo curarine blocks the myoneural junctions thus abolishing the muscular response to the electrical stimulation transmitted to the nerve from the resectoscope loop through the intact bladder wall.

3. It is our belief that this method obviates a not infrequently annoying, and sometimes disastrous complication of transurethral resective procedures.

PROFILE: EMIL NOEGGERATH, FIRST GYNECOLOGIST TO THE MOUNT SINAI HOSPITAL

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EDITOR'S NOTE. This is the third in what is expected to be a series on our great men of the past. Unfortunately, the long time elapsed has already resulted in the loss of much of the personal details these profiles are aimed at preserving. However, Dr. Goodman's incisive story gives enough to paint a picture of a man of unswerving and uncompromising integrity, championing a then socially disruptive scientific theory, saved from the fate of Semmelweis by proof of its validity forthcoming during his lifetime.

In 1869, Emil Noeggerath, a German trained physician practicing in New York City, announced his revolutionary views on gonorrhea. He claimed, on the basis of years of clinical observation, to have discovered that uncured gonorrhea in the husband and father was responsible for sickness, difficulty in labor and in due time, sterility, in his unsuspecting wife. This thesis fell on deaf ears in an era before the acceptance of the germ theory.

The best part of a decade went by. Neither German nor American physicians were impressed by the work on latent gonorrhea. The book on the experience was published in 1872 in Bonn, as "Die Latente Gonorrhea im Weiblichen Geschlecht".

Emil Noeggerath was certain that germs were responsible for the disease; he knew that gonorrhea was not cured when the obvious discharge ceased; he visualized germs hiding in the soft tissues capable of exciting reactions. No one believed him. Then, in 1879 Albert Neisser, a youth barely out of his teens, made the discovery of germs foretold by Noeggerath as the cause of gonorrhea. Each phase of the major work of Noeggerath was verified; however, the name of Albert Neisser became known to a thousand for every one who knew the name of Emil Noeggerath.

Emil Noeggerath was the son of a professor of mining engineering at the University of Bonn, a man of varied interests who was acquainted with Goethe, and whose circle of friends included scientific and literary notables of his time. The senior Noeggerath was a liberal, though it was difficult to be a liberal in his era.

The young Noeggerath graduated from Bonn as a physician in 1852. He was dedicated to work and more work. His postgraduate studies carried him to Berlin, Vienna, Prague and Paris. He married and had a family and practiced medicine in a small town on the Rhine. His was the promise of a quiet life in a quiet countryside.

An offer came to teach in a new university to be built in St. Louis, Missouri, in the United States of America. Emil Noeggerath uprooted his family and set off for the promised land. He arrived in New York in 1857, ignorant of the customs and language of the New World, without funds and ill. This illness, to plague him until his death, was pulmonary tuberculosis. In addition, disappointment



came at the moment he was leaving Castle Garden; the St. Louis project had failed. With no university position in the west, he started practice in New York City. Review of the earliest available directories of the New York State Medical Society discloses that he had an office at 125 Waverly Place. His office hours were from 8 to 9 in the morning and from 3 to 5 in the afternoon.

In 1858, Noeggerath wrote on epicystotomy for the *New York Journal of Medicine*. In the same year, he was credited with the invention of a pessary. The next year, Noeggerath (with Abraham Jacobi, long time Attending Physician and President of the Medical Board of The Mount Sinai Hospital) wrote "Contribution to Midwifery and Diseases of Women and Children". The book cost the two authors \$800.00. The unbought copies were a drag on the publishers; the authors bought the "remainders" and sold all the copies for waste paper as they lacked storage space. The book is now regarded as of "historical value, being one of the first efforts in that field".

In 1867, Noeggerath was at the German Dispensary of the City of New York, in the section of Diseases of Women. In 1869, he was elected Corresponding Secretary of the New York Obstetrical Society, and held this post for some years. He was a member of the New York Physicians Mutual Aid Society, founded in 1868.

In 1872, Noeggerath published his clinical observations in his pioneer work, "Die Latente Gonorrhoea im Weiblichen Geschlecht", appearing in Bonn. It must be recalled that the years prior to 1872 had not seen the proof of the microbic origin of gonorrhea. It was the time when acknowledged specialists held the erroneous view that gonorrhea was contagious only in the stage of purulent discharge. Men were allowed to marry as soon as the pus disappeared from the urethra. Women were thought to have gonorrhea only in the vagina and urethra.

Emil Noeggerath tried to change these views. He outlined the danger of gonorrhea to women, and drew attention to the fact that after active symptoms of

gonorrhea disappear the infection remains and is still contagious. He foresaw the presence of microorganisms within the mucous membranes as the cause of the disease. The paper explained inflammation of the uterus and the appendages as the direct result of gonorrhea. The disease was difficult, if not impossible to cure in 1872. Gonorrhea often remained latent for months or years, causing severe complications. Infection followed sexual intercourse despite long periods of apparent quiescence.

Noeggerath proved that scarcely ten women out of one hundred who became the wives of men who formerly had been afflicted with gonorrhea remained healthy. He maintained that most of the acute and chronic inflammation of the female genitalia resulted from gonorrhea. He showed not only that florid, acute, recently acquired gonorrhea or a chronic gleet on the part of the male, but a latent, quiescent and apparently disappeared gonorrhea could also infect. Noeggerath gave us the concept of honeymoon gonorrhea, with the bride becoming infected on her marriage bed. He indicated the frequency with which sterility followed gonorrhea in women, and showed that sepsis followed the labor of pregnancy when pregnancy did occur.

A Scot, Angus Macdonald, in the *Edinburgh Medical Journal* for June, 1873, strongly confirmed the view of Noeggerath. He made this prophecy: "It does not seem in the least Utopian to anticipate that some day we shall be able to see with the microscope the germs, whether they be one or many species, which give rise to the blood changes which give rise to puerperal fever and other septicemic disorders".

Carl Henning, in 1874, reported on Noeggerath's theory before the Medical Society of Leipzig. It encountered almost unanimous opposition, in which even the great Carl Crede joined.

Noeggerath formulated a variant of the Lister carbolic acid spray. For the examination of the vagina, he used a mixture of soap, glycerine and absolute alcohol to which six or ten per cent of crystallized carbolic acid was added, and he lubricated fingers and instruments with it to avoid transfer of infection.

In Germany, Noeggerath was associated with American medicine. In the United States, he was a German. His work was accepted on neither side of the Atlantic. Europeans did not then deign to learn anything from primitive America. His colleagues in America regarded the alien Noeggerath with distrust.

Noeggerath would probably have been difficult to get along with in any case. His personality was a harsh one. An inordinately tall man, lean, and described as of saturnine mien, he had an extremely critical mind and it seems to have brought him much animosity. He did not pull his punches. He was outspoken in opposition to popular post partum surgery, but surgeons continued to operate on cervical tears.

Emil Noeggerath had no illusions. He began his address at the Inaugural of the American Gynecological Society held at the Academy of Medicine Building, New York, June 3, 1876, with these words: "In the year 1872, I published in the German language a monograph on latent gonorrhea, which was not received very favorably by the medical press. The suggestions laid down were so

new, and so contrary to the theories prevalent at that time, that the book was looked upon with distrust". Noeggerath restated his case. He remained one of the great pessimists as to the prognosis for the eventual well-being of the patient with gonorrhea and its consequence to sexual partners.

He was denounced. Read the remarks of the presiding officer: "The well known character of Dr. Noeggerath as a conscientious and scrupulously careful observer, must inspire great respect for him in the minds of all, but he must anticipate that such views as are set forth in his papers, so startling in the present state of the morals in society, will receive the most careful scrutiny. If these views are true, a modification of this paper should be found in every Sabbath school library throughout the land. I know not whom to call upon to take part in discussing this subject, and therefore shall ask for the expression of opinions from such members of the Society as are familiar with the phenomena mentioned in the paper".

Dr. Trenholme of Montreal rose to say, "On behalf of this continent, at least as far as area is concerned, I feel that I should call for protection from the doctrines of this paper. We, upon our side of the line, look upon it rather as a reproach not to have a large family; and if our Canadian ladies found out that their sterility was dependent upon the former conditions of their husbands, I do not know what would take place."

"With regard to the gonorrhea germ", continued Dr. Trenholme of Montreal, "and its effect before marriage, there is probably something of value in the paper, but that the disease is continuous in its effect, and does a perpetual work, I am not ready to believe".

Dr. Engelman said, "Dr. Noeggerath's paper explained some facts which I have repeatedly seen in postmortem examinations but have not understood. . . . But I must be allowed to say . . ." Dr. Engelman found much left unexplained and attempted to destroy Noeggerath's contentions.

So it went. Dr. Noeggerath closed the discussion. "I perceive that the contradictions which have been raised, are based upon a few single facts. The theory which I propose requires careful study and a great deal of experience for its recognition." He finished, "After the gentlemen have given five years or more to careful study of this question, I shall expect to hear more approval than I have heard today".

Emil Noeggerath was appointed gynecologist to The Mount Sinai Hospital in 1877. This was one of the original steps leading to specialization within the in-patient hospital service. He remained at Mount Sinai until 1882, functioning as chief of the gynecological service, the first in a distinguished line, to be followed by P. Mundé, F. Krug, H. N. Vineberg, J. Brettauer, R. T. Frank, I. C. Rubin, S. H. Geist, M. A. Goldberger, and A. F. Guttmacher. It is to the credit of the Hospital that this stormy petrel and then controversial figure was recognized and given preferment prior to his vindication before the world which followed Neisser's discovery of the gonococcus and the bacteriological and pathological studies of Bumm, Sanger and Wertheim.

Noeggerath made studies of the problem of vulvovaginitis in children. He described complications in the system, as pyosalpinx, endocarditis, etc. He evalu-

ated promised cures and found them wanting. He sought to secure finite differential diagnosis of vulvovaginitis of gonorrhea and other origins prior to the demonstration by Neisser of the gonococcus in 1879.

Noeggerath was fortunate in having Neisser's discovery come when it did. It enabled Noeggerath to confirm his clinical work by exact laboratory research and rescued him from attack and abuse. Ernst von Bumm (1858-1925), one of the first to culture the gonococcus, wrote: "Noeggerath was more fortunate than Semmelweis; he lived to see the triumph of his observations. For this he has to thank Neisser, who soon after discovered the gonococcus and made possible the certain proof of his statements relative to the frequency of the lesion."

R. Franz wrote in the *Handbuch für Dermatologie und Syphilologie*, Vol. XX No. 1, page 556: "Seine Lehre erfuhr vielfach Widerspruch und er selbst wurde wegen desselben so angefeindet dass er seine Arztliche Tagigkeit in New York aufgeben musste".

Emil Noeggerath returned to Germany in 1885, where he settled in Wiesbaden. Although his health was poor, he continued scientific research. In 1887, he suggested that bacteria might be isolated by growing them in gelatin to which aniline dyes of different color reactions had been added.

Noeggerath investigated new growths. He published, in 1892, "*Beiträge zur Struktur und Entwicklung des Carcinoms*". He found no confirmation of the parasitic theory. He proposed far in advance of his time a theory of carcinoma genesis which emphasized the importance of nuclear substances.

Little more is found regarding Noeggerath. He died May 3, 1895. A diligent search of the obituary columns of the medical magazines for 1895 and 1896 disclosed one brief reference. The *Medical Record* for May 25, 1895 stated: "Professor Emil Noeggerath died May 3rd at his home in Wiesbaden after a long and painful illness".

THE PSYCHODYNAMICS OF PROFICIENCY AND DIFFICULTY IN READING HANDWRITING*

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This paper attempts to demonstrate that illegible handwriting evokes certain discernible conscious and unconscious emotional reactions in the reader. The content of the text appears to be a more important determinant in bringing out resistances and distortions in the reader than the chirographic characteristics of what is written. In other words, *what is written takes precedence over how it is written.*

Varying degrees of illegibility have been chosen for the test material, since typewritten or even Spencerian script lowers the threshold of resistance to such an extent that the manifestations of resistance and distortion on the part of the reader are often masked by over-compensation and reaction formation, or on the other hand, are too minimal to be detected easily. Therefore, in this experiment nine paragraphs were composed, the first of which was designed to be bland and neutral. This was used as a control. The other eight paragraphs were designed to tap a variety of psychosexual levels in accordance with psychoanalytic principles. In order to obtain different degrees of illegibility, some 20 people were asked to copy typewritten samples of all nine paragraphs. They were requested to make no particular effort to write legibly or illegibly and were also asked to copy each paragraph on a separate card. These contributors were told nothing about the objectives and were deliberately chosen because of the authors' previous acquaintance with each person's particular handwriting. It was, therefore, thought that the variability of their productions would be sufficiently diverse for the purposes of this experiment. It should be emphasized that these contributors were not the subjects of these tests but merely furnished the tools for the experiment. The following are the nine tests:

- 1—*Bland and neutral*: It is very kind of you to cooperate so graciously. You have thus added to our knowledge concerning experimental material which we hope may prove to be of some value.
- 2.—*Oral*: The food would make your mouth water. We gorged ourselves on pies and cakes, roast geese, eating and drinking until we could hold no more; it was truly a land running with milk and honey.
- 3—*Oral-sadistic*: It was an argument I could sink my teeth into and chew into shreds; regardless of his snarls and backbiting comments at the end of ten minutes the torn and ripped bits of his defense littered the floor.

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- 4—*Oral-passive*: Like a little infant blissfully suckling at its mother's breast, its face rosy with ecstatic gratification and no other sensation in the world save the constant flow of warm milk.
- 5—*Anal-erotic*: Filth and dirt everywhere, the floor littered with garbage; cockroaches scampering over the wall, the odor of urine and feces; mud roads.
- 6—*Anal-retentive*: Secret documents of a suspicious nature warrant caution in the investigation. Mum's the word and trust no one. If you know something keep it to yourself.
- 7—*Anal-sadistic*: Messing up the lives of others, they deserve to have their own lives messed up. Let mud be smeared over their own reputations so that they can experience the stench of defamation.
- 8—*Phallic*: They loved each other with both tenderness and passion sharing to the full of the union of their flesh and dissolving together in the bliss of climax.
- 9—*Regressive-urethral*: The glory of the sunset. The darkening sky aflame! So vividly contrasting with the dim pastel decor of the "Bon Soir", the boite in Montmartre where so many hours of escape had been wasted.

All subjects to whom this test was administered possessed at least average intelligence and were to the best of the authors' knowledge free from any reading disability.

The 6 subjects who were tested in this experiment were private patients of M. G. This test was given to them by him in the course of a therapeutic session. By contrast, F. B. administered a variety of samples in a non-therapeutic atmosphere, namely in the course of giving the routine battery of psychological tests. This was done without any previous consultation with M. G., and therefore F. B.'s findings were completely independent and unbiased.

Thus each patient was presented with the test material by the two examiners. This double testing was done deliberately in order to discount the particular difficulty or facility that any one person might encounter with any one sample. Also, in having two examiners test the same subject the influence of the transference could be more accurately estimated.

Some of the readers had great difficulty in reading the paragraphs but made no overtly critical comments about the handwriting. Others demonstrated greater fluency and proficiency but assailed the writer in no uncertain terms. Another reader resorted to humorous scoffing and mocking solicitude ("they should get a typewriter"), and this same man overwhelmed the examiner (F. B.) with detailed and endless responses in the Rorschach while he inquired from time to time, "Am I wearing you out?", followed by antithetical resentment, saying, "You should learn shorthand", and, "Why don't you get a tape recorder?"

If we now compare certain types of misreading we note that each reader apparently has his or her own shibboleths and that what is one person's undecipherable script is quite obviously easily read and meaningful to another. Some readers will guess at a word, while others will judiciously skip it without such an attempt. It is possible that persistent efforts to read a text which soon make no sense because of the substituted words might represent an unconscious need

to alter the sense of the content even to the extent of "jamming" the passage. These reactions give some indication of the various ways in which the task is approached, suggesting that personality correlates may be involved.

A. A single white man of 32 whose latent homosexuality, unresolved oedipus complex, terror of women and enormous dependency needs are conspicuous psychiatric features, when given 2 different samples by his therapist, read "defecation" for "defamation" (paragraph 7) in both samples. When 2 different samples were presented by the examiner, he read "mud roads" respectively as "mud loads" and "mud wads". In his Rorschach he made frequent reference to "rear ends" and revealed a shift from oral to anal attachments in his serial Rorschach.

Before administering the test, the psychiatrist predicted that this patient's patent anality would show itself in resistance to an ensuing difficulty with paragraphs 5 and 7. This was clearly demonstrated in all the different samples administered by the two authors.

B. A white married man of 41, the father of 3 young sons, is married to a woman 20 years his junior. He is also the junior partner in a highly successful mercantile firm. His attitude of filial dependence towards any and all authority and his endless self-reproaches thinly mask his intense hostility to those persons who force him to accept the hateful role of an adult with its ensuing responsibility. Analogously his peremptory sexual demands run parallel with a low degree of potency. When denied immediate sexual gratification he feels abused, sulks and finally bogs down in a morass of self-pity coupled with overt hostility towards his wife.

Since this man is incapable of sharing in many of his interpersonal contacts and since his psychosexual functioning is clearly arrested at a pregenital level, it was predicted that he might run into difficulties with paragraph 8. This was born out by the fact that on all 4 samples (again administered by the 2 examiners) he consistently read the word "sharing" as "showing". He had no difficulty with oral receptive and genital material by the same writer with whose anal paragraph he struggled unsuccessfully, extricating himself only partially by altering "urine" to "wine" (all 4 samples). His Rorschach also brings out a sharply delineated anal character.

C. An unmarried white man of 32 can best be described as "un vieux garçon". He is a talented and successful commercial artist of superior intelligence. Born in Europe, he has mastered the English language remarkably well in his 15 years in America. He lives at home with his aging parents, blames them for his failure to marry, "date" girls and inability to indulge in anything except the most constricted social intercourse. His obsessive and compulsive characteristics plus a marked hypochondriacal trend are outstanding. Although he has been most productive in therapy in discussing his sexual problems, he conspicuously and consistently by-passed his relationship to his father, which was particularly noticeable since he was extremely vehement in voicing his resentment towards his mother whose chronic ill health he holds responsible for his failure to emancipate himself from the parental clutches.

It was predicted by the therapist that some of the repressed material concern-

ing the father might emerge in the test material. To the amazement of his therapist he read all samples with unusual ease and fluency except the last phrase of paragraph 2, "a land running with milk and honey". In both samples he was unable to read these words, simply skipping them as if they were non-existent. No comment was made by the therapist. However, in the course of the next 4 or 5 visits he began for the first time in the 4 years of therapy to talk spontaneously and freely about his father. It became clear that: (1) his father had for years tried to inflict his own Jewish orthodoxy on the patient; (2) recently the father because of severe arteriosclerotic frontal lobe softening had taken to "running around", making it frequently necessary for the patient to search the neighborhood for him. This often proved embarrassing, since he frequently found the old gentleman wandering into strange homes and shops. At such times he would often find his father reading excerpts from the Old Testament, and he recalled seeing the phrase "a land running with milk and honey" on the page of the Bible which his father promptly snapped closed at the moment his son came to fetch him. In this case the traumatically charged material having to do with a biblical quotation plus the association of the word "running" with his father's unwelcome peregrinations served as a most useful therapeutic wedge in promptly lowering the patient's resistance to the point where he found it possible and useful to discuss an important and hitherto repressed topic. It is interesting to note that the psychologist knowing nothing of the above at the time made the following observations. He notes the reader to be gently masochistic preferring to skip difficult material completely. On the oral-sadistic material he altered "ripped" to "ruffled" and "argument" to "apartment". (This mistake was also made when tested by the therapist and clearly had to do with the conflict he had about living at home—his parents' apartment.) His sexual confusion is projected in the distortion of "his" for "hers" (again bringing out repression regarding his father) and after giving up on the oral-receptive paragraph, he misread "cockroaches" as "cock-suckers". The Rorschach showed strong evidence of a disturbing and disruptive latent homosexuality and also re-emphasizes consistently his distortions of gender.

D. An unmarried diabetic white woman of 30 lives at home with a domineering sadistic mother and a passive "milquetoast" father. She is an only child, has been diabetic since she was eight, and some 4 years ago developed recurrent episodes of pseudocyesis, which after prolonged analytic study was demonstrated to be unconsciously conditioned. She has consistently neglected her diabetes, deliberately taking inadequate doses of insulin and also picking at her toes until trophic sepsis developed—all this in spite of constant competent medical surveillance and several protracted hospitalizations. She is a repressed, narcissistic woman who regards herself as a little girl. She has been unable to even contemplate genitality and although she prattles vaguely about the possibility of marriage, it is clear that this represents merely a social escape from the onerous confines of her parents' home. There has been only the most sporadic "dating" resulting in each instance with successful rationalization to the effect that "the man is not right" and therefore even this superficial association can be legitimately terminated.

She is truculent and resistant to any therapeutic suggestion, and yet shows a paradoxical lack of aggression.

It was predicted that her preoccupation with food coupled with her oral impregnation fantasies would bring out resistances to paragraph 2. It was also predicted that the intense hostility to her mother (requiring introjection to overcome which partially explains her pseudocyesis) would somehow come out in the test material. In paragraph 2 she misread "mouth" as "land" in both samples administered by the therapist and in paragraph 6 twice completely skipped the word "mum's", making no comment at the time for the omissions but embarking at once during the balance of the psychotherapeutic hour on a more vehement and detailed invective and itemized many more complaints about her mother than she had ever indulged in during the 5 years she has been in therapy. Never before in any area at any time had she been able to mobilize anything resembling such aggression. This she maintained for the next 2 visits and at the third announced that she felt "a lot better" and that her "tummy was down" (pseudocyesis ameliorated).

On psychological testing it is noted that the Rorschach showed evidence of a weaning trauma which apparently generates outstanding nurturance drives (Rorschach percepts: brains, tripe, sweetbreads, sherbet, lambchops; Word Association Test: mouth "eating", stomach complete block followed after 36 seconds by "tube" and "tripe"). The psychologist comments "she craves benefits and is a strikingly oral individual". Where 3 samples of handwriting are shown this patient by him, she showed excellent reading of the oral material except for the distortion in 2 of the samples of the word "mouth" to "land" but relinquished the task on the oral-sadistic paragraph and also performed very poorly on all the anal-sadistic material.

E. A 30 year old white married man whose vocation involves food shows in his Rorschach a strongly entrenched homosexual component with a heterosexual facade utilizing possible pseudo-hypersexuality, manifested by a phallic aggressive attitude toward women coupled with strong urethral components. His underlying strong oral cravings have alcoholic additive implications (on the "mother" card, VII, "pieces of bread broken up" and "two young lambs suckling their mother"). He was unable to read the word "sharing" on the genital selection, an interesting reflection of his own inability to do so; read "assiduous" for "gratification" on the oral-receptive paragraph and did very poorly on the anal-retentive material, failing the words "suspicious" and "secret". Clinically, he tries to give the impression of being friendly and genially compliant. His outstanding performance was accomplished with the food paragraph. His failure to read "suspicious" and "secret" was predicted since this man, in spite of his obvious paranoid tendencies has managed to obtain a permit to carry a revolver at all times. He is constantly presenting his therapist with an endless series of blood and thunderswashbuckling incidents in which he always emerges the hero. He "suspects" everyone, has no friend he can really trust. The core of his problem is the raging conflict between esthetic and artistic notions and his exhibitionistic and aggressive swashbuckling. He regards the sensuous pursuit of esthetic pleasure as

"secret" and feels an awareness of these aspects of his personality by others would constitute an unwelcome exposure.

F. A 29 year old single white man who is a public accountant was referred to the therapist because of a suspended court sentence for voyeurism. He is an inarticulate, diffident, small-voiced man whose lack of ambition and bland complacency reflect his basic timidity and almost total lack of insight. His ambitions are extremely limited, and his intelligence only fractionally mobilized. His striking resistance to any and all therapeutic interpretations runs parallel to his outstanding filialism. He is terrified at self-exposure and in order to minimize this catastrophe adopts an extremely efficient insulating defense including omnipresent denials whenever he is confronted with what he considers to be a challenging question. His aggressions are extremely limited, and his mood is consistently one of bland almost colorless affect. His apathy shows itself in a lack of fantasy productions and an almost total lack of humor. His reminiscences are brief, sketchy and devoid of detail and convey no emotional over-tones. There are both paranoid and schizoid trends. He also shows a conspicuous lack of inner resources, interests and drives. The need to defend himself is an all powerful and demanding necessity so that a large part of his energy and productions consists in repetitive attempts at self-justification. This patient was in therapy only 5 weeks, since after the psychological and psychiatric reports were forwarded to the court he was put on probation. Immediately after, contrary to his original expressed intention, he placed himself in the hands of a lawyer who telephoned the therapist stating that the patient no longer wished to continue treatment. In contradistinction to the other readers the therapist did not attempt to predict what this man's performance would be with the test material, since there was no basis for such prognostication in dealing with such an overt voyeurist. The therapist was amazed, therefore, when the patient read all 9 paragraphs without hesitation or error. None of the other readers even approached such unusual facility. It seemed reasonable to correlate this exceptional performance with the patient's scopophilia although it might have been equally likely that this compulsion could have made him a very poor reader.

The psychologist reports as follows. "This patient is the best reader of the most illegible writing samples we have had to date. He had no difficulty with any content level and read several paragraphs perfectly. His only distortion occurred on the phallic paragraph where he read 'they loved each other not endlessness and passion', an interesting error in view of his probable skepticism over the permanence of heterosexual relationship, his denial of passion, and his inability to feel other than sadistic impulses toward women who are all derivatives of the mother figure (his drawing of a house was first seen as in sunshine but was spontaneously altered to 'covered with snow, and the scenery covered up so you can't see much'). We can't say, therefore, that voyeurs will have difficulty reading our samples. On the contrary, stripped of such symbolism as the TAT presents, and offered as a 'homely' task, the scopophilic wish seems to take precedence over neurotic or characterological defenses and breaks through in an uninhibited form. Among other manifestations of scopophilic denial in the test battery, he failed

to see the violin on Card I of the TAT and commented that the boy in the picture 'has one eye open, thinking of other things, day-dreaming, ready to go to sleep'; while on the sex card of the same test (13 MF) he completely repressed the strong sexual implications of the scene and remarked, 'The outcome is that the man will probably go to sleep . . . I mean go to work and so sleep on the job'."

These reports of 6 patients serve as a nucleus for further studies. Some 16 others have also been tested with comparable findings. It has been suggested to the authors that dealing with illegible handwriting is comparable to the most abstract kind of thought which can be considered at the highest level of ego functioning and that this material also represents a challenging type of intellectual process. It was also indicated by several of the authors' colleagues that at just such a level of highest intellectual functioning should be found early disturbances, and this has actually been the case in these clinical testings. It has also been mentioned that this test has value as a kind of probing instrument since one is dealing with symbols of changing values.

It might be assumed, after reading the content of the stimulus paragraphs, that the material is too patent and direct and that a more subtle approach, perhaps on a symbolic level, should have been attempted. In countering this assumption, it should be pointed out that what is too direct for the psychological sophisticate still remains abstract to the innocent reader so far as insight into the underlying meanings are concerned. It should be pointed out that the varieties of pornographic literature are famous for their directness and that such literary gems as *Opus Sadicum*, *Nell of Bridewell*, *Venus in Furs*, the *Decameron* and the *Abby Brantôm's* tales appeal to and stimulate such readers as are attracted to the genre. *Nell of Bridewell* might not appeal to a genitally mature individual. It can be assumed further that avid readers of *Gourmet* magazine, *Cordon Bleu* menus, and descriptions of *Lucullan* feasts will hardly show themselves as rigid anal characters on the *Rorschach*.

Finally, it should be noted that the *Blackie Test* is based directly upon the various stages of psychosexual development, ranging from oral-receptive to selection of a love object. The pictures are almost literal representations of each phase, the only disguise consisting in the fact that dogs instead of humans are portrayed. Again the "obviousness" of the material lies in the eye of the beholder, who, if psychologically sophisticated, can only wonder at the manner in which patients, both children and adults, expose themselves on what is considered "sensitive" content.

SUMMARY

The authors are impressed with the striking variations manifested in reading and comprehending handwriting, both legible and illegible. In order to evaluate such variations in reading ease and difficulty, selected samples of handwriting are used, the texts of which are "loaded". As a control a bland text composed by the same writer as the loaded samples is presented to each subject. It should be emphasized that the writers of the text which constitute the samples employed were in no instance the subjects tested. Observations are then possible concerning

the difference in the reader's proficiency in reading and understanding both texts. The "loaded" texts are specifically composed to represent emotional content typical of various psychosexual levels.

It is believed that this material constitutes the basis for a new and valid projective technique, and since it can be administered and evaluated quickly, it is hoped that it may find a place as an addendum to the battery of psychological tests now routinely employed. This test also seems useful in therapy, since in several instances it has acted as a wedge, uncovering unconscious and conscious resistances of the patient, thereby permitting him to embark with relative freedom upon topics which had hitherto been either minimized or totally omitted.

PREGNANCY COMPLICATED BY IDIOPATHIC HYPERLIPEMIA AND IDIOPATHIC HYPERCHOLESTEREMIA*†

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In normal pregnancy there is a moderate increase in concentration of all serum lipid fractions (1-6). This paper is concerned with the association of pregnancy with inborn errors of lipid metabolism, idiopathic hyperlipemia and idiopathic hypercholesteremia. The metabolic disorders are characterized by elevation of various serum lipid fractions (7).

Two women, each with one of these disturbances of lipid metabolism, were followed at Mount Sinai Hospital during pregnancy, delivery and the puerperium. One woman had idiopathic hyperlipemia with two attacks of acute pancreatitis occurring late in pregnancy. The second patient had idiopathic hypercholesteremia, with xanthelasma, xanthoma tendinosa and coronary artery disease. Because of the rarity of these diseases and their complications in women of the child-bearing age, it was deemed worthy to report the observations made during and after gestation.

IDIOPATHIC HYPERLIPEMIA

Case 1. A 25-year-old Puerto Rican woman was admitted to The Mount Sinai Hospital during the 36th week of pregnancy because of mid-epigastric pain and severe vomiting of 24 hours' duration. The patient was first seen in prenatal clinic at 27 weeks' gravidity. Past obstetrical history included three uneventful full-term deliveries and one spontaneous abortion necessitating dilatation and curettage; none of these pregnancies were followed at Mount Sinai Hospital. Physical examination in the clinic had revealed no abnormalities other than an enlarged uterus consistent with the gestational age. The blood group was O and the Rh factor, positive. Because of the milky appearance of the serum, lipid determinations were performed. The results are listed in Table 1. The normal non-pregnant lipid values and the normal peak values for pregnancy are presented for comparison. All lipid fractions were increased, particularly triglycerides and total lipids.

The patient had remained well until the 32nd-33rd week of pregnancy, when she suffered a 3-day episode of mid-epigastric pain, occurring about one hour after meals and at night. The pain was aggravated by lying down. There was some nausea, but no vomiting. She was given belladonna with relief of pain. The patient was asymptomatic until her hospitalization. Epigastric pain recurred approximately 28 hours prior to admission, accompanied this time by severe nausea and vomiting of green non-bloody material.

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TABLE 1
Blood analyses in patient 1, idiopathic hyperlipemia

Time	Remarks	Appear- ance	Cholesterol		Phos- pholipids	Trigly- cerides	Total lipid	Amylase	Bili- rubin
			Total	Esteri- fied					
			mg per 100 ml					Somogyi units	mg. per 100 ml
Preg- nancy— 27 weeks	free diet a- symptomatic	milky	498	264	660	2952	4110		
36 weeks	abdominal pain vomit- ing	cloudy	254	158	386	570	1210	204	294
38 weeks	abdominal pain vomit- ing	cloudy	410	219	—	—	—	137	1.2
Post-par- tum day 1	NPO	cloudy	323	188	478	769	1570		
day 8	reg. diet asympto- matic	milky	297	170	436	1392	2125	71	0.93
day 17 22	reg. diet asympto- matic	milky	296	174	500	834	1630	48	
day 42	reg. diet asympto- matic	milky	212	145	348	—	—		
day 102	10 days fol- lowing ab- dominal pain	milky	246	148	388	1896	2530		
Normal (7)	fasting	clear	210	160	250	240	700		
Peak preg- nancy (5)	fasting	clear	276	204	398	292	966		

On admission her temperature was 100°F. and pulse 96. The patient was acutely ill, restless and dehydrated. There was marked epigastric tenderness to deep abdominal pressure, but no rebound tenderness or rigidity. Urine examination revealed pyuria and 4+ acetoneuria. The patient was treated with sedation, anti-emetics, intravenous fluids and gantrisin.

The day after admission the patient continued to vomit despite symptomatic therapy. In addition to the pain in the epigastrium there was beginning left flank pain with radiation to the shoulder. Chemical analyses of the serum revealed a CO₂ combining power of 4.8 meq/l, Na 128 meq/l, Cl 103 meq/l, K 4.6 meq/l and a BUN of 8 mgm. %.

The following day, pain and tenderness were still present but the patient was able to drink clear fluids. Serum amylase level was 204 Somogyi units (normal less than 150). In view of the diagnosis of acute pancreatitis, intravenous fluids were continued and intramuscular achromycin and pro-banthine were added to the therapy.

The next day the abdominal tenderness had decreased. There was a sub-icteric tinge to the sclerae. Chemical analyses including serum lipid determinations are listed in Table 1. The patient had been fasting and receiving only intravenous fluids for several days prior to the time the lipid determinations were performed. All levels were lower than before but

were still abnormal. The CO_2 combining power was 20 meq/l. There was a faint trace of bile in the urine and urobilinogen was present in dilutions of 1/20.

The patient improved rapidly thereafter. The pro banthine was continued orally. The bilirubinemia decreased. She remained asymptomatic in the hospital for two weeks, when she had a recurrence of epigastric pain and vomiting. Blood studies performed the day after the relapse showed a rise in cholesterol and amylase with slight increase in bilirubin (Table 1). She recovered within two days. At this time she was approximately one week from term. The cervix was favorable and induction of labor was accomplished by intravenous pitocin and amniotomy.

The post-partum course was uneventful and the patient remained well. Serum lipid determinations done on post-partum day 1 after four days of intravenous fluid with nothing by mouth are presented in Table 1. Studies done on postpartum days 8, 17, 42 and 102 with the patient on a regular diet and ambulatory are also included. The serum was persistently milky with increased levels of triglycerides and total lipid. Serum amylase values which were elevated during episodes of abdominal pain had returned to normal. Roentgenological examination of the gall bladder and the upper gastro-intestinal tract revealed no abnormalities. The electrocardiogram was normal. Eye ground examination had not shown lipemia retinalis at any time. Pancreatic enzyme studies performed on the tenth postpartum day were within normal limits. Lipid studies of serum from the patient's mother, father and several siblings were all within normal limits as were studies on the cord blood of the newborn infant.

In summary, a young Puerto Rican woman with idiopathic hyperlipemia was observed during pregnancy complicated by recurrent episodes of pancreatitis.

IDIOPATHIC HYPERCHOLESTEREMIA

Case 2. A 33-year-old white female was admitted to the hospital because of early pregnancy complicated by increasingly severe precordial pain. The past obstetrical history included two uneventful full-term pregnancies at another institution, the last eight years prior to the present admission. Following that delivery, she developed a secondary amenorrhea until 18 months prior to the current admission, when regular menstrual periods re-established themselves spontaneously. During the 6 year period of amenorrhea, her weight rose from the usual 130 lbs. to 208 lbs. Four months prior to admission, the patient's menses suddenly ceased. The amenorrhea was accompanied by nausea and vomiting. An A-Z test was positive.

Three years before admission, on exposure to cold or exertion, the patient developed substernal pressure without radiation. Initially the attacks occurred infrequently, but by the time of admission they had increased in frequency and intensity. Nitroglycerine at first was effective in relieving the pain but had become less so.

Physical examination on admission revealed an obese female (weight 165) with xanthelasmas of the eyelids and xanthoma tendinosa of the Achilles tendons and extensor tendons of the hands. The blood pressure was 120/70. (The referring letter from her private physician stated that she was occasionally hypertensive). A grade IV apical systolic murmur and a grade II basal systolic murmur were present. On pelvic examination the uterus was enlarged to a size consistent with a 12-16 week gestation.

Serial electrocardiograms revealed changes in the T waves and ST segments which were indicative of recent myocardial involvement. Serum lipid studies are listed in Table 2 and were characteristic of idiopathic hypercholesteremia with marked elevation of total and esterified cholesterol and lesser increase in the other lipid fractions. There was no evidence of any disease which per se would result in hypercholesteremia.

Her father had died at age 67 of a coronary thrombosis; one brother had the physical stigmata of idiopathic hypercholesteremia including xanthoma tendinosa and bilateral arcus senilis, and the characteristic serum lipid abnormalities. The patient's paternal cousin died suddenly at age 42, presumably from coronary thrombosis. A paternal uncle died at age 30, cause unknown.

TABLE 2
Serum lipid partition in patient 2, idiopathic hypercholesteremia

Time	Remarks	Appear- ance	Cholesterol		Phos- pho- lipids	Trigly- cerides	Total lipid
			Total	Esterified			
mg per 100 ml							
Pregnancy							
14 weeks	Xanthelasma, xan- thoma tendinosum, angina, 165 lbs.	clear	515	361	422	443	1380
28 weeks	Low fat diet	clear	482	322	454	564	1500
36 weeks	Low fat diet, 150 lbs.	clear	510	407	—	—	—
2nd stage labor	150 lbs.	clear	512	394	480	698	1690
1 yr. post-par- tum	Reg. diet, 178 lbs.	clear	462	342	536	267	1265
Normal	Fasting	clear	210	160	250	240	700
Peak pregnancy	Fasting	clear	276	204	398	292	966

The decision was made to allow the patient to carry to term because interruption of pregnancy at that stage would have necessitated an abdominal hysterotomy. The patient was referred to the prenatal clinic where she was followed frequently by the obstetrical and cardiac consulting staff. She was maintained on a strict fat free, low calorie diet. During the pregnancy, she lost 15 lbs. Lipid determinations at 28 weeks' gestation are recorded in Table 2. Serial electrocardiograms revealed no changes from the previous tracings. During the pregnancy, she experienced infrequent episodes of substernal pain.

The patient was hospitalized again approximately one month from term. Lipid values at that time were unchanged (Table 2). Five days before her due date she went into labor. After three hours she delivered a 2700 gm. infant spontaneously under a pudendal block. Lipid values were obtained late in the second stage of labor. Lipid studies on the cord blood of the newborn infant revealed an elevated total cholesterol of 148 mgm. % (normal cord blood level 70 mgm. %). The patient had an uneventful postpartum course. Serum lipid values obtained twelve months after delivery were lower than those obtained during the pregnancy despite the patient's gain in weight to 178 lbs.

In summary a patient with familial idiopathic hypercholesteremia with its characteristic genetic, clinical and chemical manifestations, was studied during a pregnancy.

DISCUSSION

There is a rise in all lipid fractions in sera from pregnant women. The rise begins at about the third month and is gradual, with a sustained peak reached at about the 33rd week which is maintained to delivery. The magnitude of the increase amounts to about 50% of the lipid levels obtained in non-pregnant women (1-6). In patient 1, the highest levels of all lipid fractions were obtained when she was asymptomatic, on a regular diet, at the 28th week of her pregnancy. Similarly, the lowest levels of cholesterol and phospholipids were obtained in the postpartum period under otherwise similar conditions (Table 1). In patient 2 lower levels of cholesterol, triglycerides and total lipid were obtained in sera drawn in the post-partum state, despite the gain in weight and unrestricted diet (Table 2).

In persons with idiopathic hyperlipemia, marked restriction of the dietary fat intake is followed by a fall in serum lipid levels (7). This effect was observed in

patient 1 in that all lipid fractions were lower after a 4-day period without any oral intake during the first episode of acute pancreatitis (Table I).

An association of acute pancreatitis with pregnancy has been reported with increased liability to recurrent attacks during pregnancy and puerperium (8-10). In addition, persons with idiopathic hyperlipemia are subject to recurrent attacks of acute pancreatitis (11, 12, 10, 7). The combination of both conditions, however, has not been previously reported. Millen *et al* described a pregnant woman who sustained an episode of acute pancreatitis 2 days before delivery and was noted to have hyperlipemia (13). Because of lack of previous data concerning the patient's serum lipids, Millen *et al* did not classify the patient as one with idiopathic hyperlipemia. The persistence of serum lactescence as well as high total lipid levels after pregnancy is compatible with the diagnosis of idiopathic hyperlipemia in their case. It would seem then that idiopathic hyperlipemia and pregnancy both present predisposing factors for the increased incidence of acute pancreatitis and that the hazard of this occurrence should be borne in mind. The recognition of idiopathic hyperlipemia in a pregnant woman should be an indication for strict restriction of the dietary fat intake in an effort to lower the serum lipid levels which would otherwise have a tendency to rise even higher.

While patient 1 with idiopathic hyperlipemia did not exhibit any of the external stigmata of the disease (i.e. xanthoma tuberosum or eruptive xanthoma), in patient 2 with idiopathic hypercholesteremia there were both xanthelasma and xanthoma tendinosa. The complicating feature in this pregnant patient was coronary artery disease as manifested by angina pectoris. Coronary atherosclerosis was the most frequently noted clinical abnormality in persons with idiopathic hypercholesteremia (7, 14) but is rarely encountered as a complication of pregnancy (15). The familial nature of this disorder was exemplified in this patient by a brother who had idiopathic hypercholesteremia, arcus senilis and xanthoma tendinosa.

SUMMARY

Two women with disorders of lipid metabolism, idiopathic hyperlipemia and idiopathic hypercholesteremia have been observed during pregnancy and the puerperium. In the first patient recurrent episodes of acute pancreatitis occurred late in pregnancy. The association of this complication both with pregnancy and the disturbance of lipid metabolism has been discussed. The second patient had coronary artery disease, a common manifestation of idiopathic hypercholesteremia but a rare complication of pregnancy. In both instances, serum lipid levels during pregnancy were higher than those noted post-partum. This was correlated with the previously observed elevation of levels of all serum lipid fractions in normal pregnancy.

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BILATERAL PLEURAL EFFUSION

ITS SIGNIFICANCE IN ASSOCIATION WITH A HEART OF NORMAL SIZE

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INTRODUCTION

For many years we have been impressed by the fact that, in a considerable number of cases, bilateral pleural effusions have been wrongly ascribed to congestive heart failure by the clinician at his first examination. Confronted with the presence of a bilateral pleural effusion without any obvious cause in a patient who exhibits respiratory difficulty, or who has a history of dyspnea on exertion, it is understandable that the first thought would be that cardiac failure is responsible for the fluid in the pleura. When, in addition, there is generalized anasarca, enlargement of the liver and distention of the neck veins, the impression of congestive heart failure is strengthened. While this diagnosis proves to be correct in most instances, not infrequently further investigation proves that the pleural effusions are due to some other cause, and that cardiac failure played no part in the production of either the bilateral effusion or the other clinical manifestations. In some instances the original error in diagnosis is not rectified until an autopsy discloses the true state of affairs.

Our experience has left us with the impression that a consideration of the size of the heart, as seen on the roentgen examination, is most helpful in differentiating bilateral effusions of cardiac origin from those which are due to other causes. It is true that a patient with an enlarged cardiac shadow may develop a bilateral pleural effusion which is not due to congestive heart failure. Thus in a case of polyserositis the cardiac shadow may be enlarged as a result of a serous pericarditis, and the pleural effusion is caused by a pleuritis which is part of the generalized polyserositis. Furthermore, a patient who has an enlarged heart from any cause may develop bilateral pleural effusions from neoplastic disease or pulmonary infarction. Admittedly, the differential diagnosis between cardiac failure and some other cause for the pleural effusions, is difficult in such instances, and the enlargement of the cardiac shadow may serve to inject a coincidental factor which adds to the difficulty in diagnosis.

On the other hand, our observations over a period of years have led us to believe that the finding of a heart of *normal size* is most helpful in the differential diagnosis. We have gained the impression from our experience that bilateral pleural effusions are rarely caused by congestive heart failure if the heart is found to be of normal size on roentgen examination. This experience has led us to search most diligently for some other condition whenever the heart was found to be of normal

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size, no matter how closely the clinical picture simulates congestive failure. In order to test this impression, we have reviewed our cases of bilateral pleural effusion in which the heart appeared to be normal in size.

MATERIAL AND METHODS

During the routine reporting of roentgen films of the chest at The Mount Sinai Hospital, a notation was made of cases exhibiting a bilateral pleural effusion, and in which the heart shadow was normal in size. We eliminated from this study the cases in which there was questionable cardiac enlargement, leaving only those in whom it was clearly evident that the heart was not enlarged. In some cases, the boundaries of the heart could not be definitely determined because of the obscuring pleural effusion. Aspiration of the fluid from one or both pleural cavities was then accomplished and the chest x-ray examination was repeated. If the heart then appeared normal in size, the case was included in our study. The clinical and laboratory data were then analyzed in order to determine the etiology of the effusions.

The study does not include cases in which the effusions were demonstrated only at necropsy. These were omitted intentionally. Since the effusions were not demonstrated clinically, these patients did not present the diagnostic problem at hand. Furthermore, bilateral effusions occurring agonally are found so frequently at autopsy that they have little significance from a diagnostic point of view.

A total of 78 cases of bilateral pleural effusions with a normal sized cardiac silhouette was thus collected, and in almost all of them a definite diagnosis as to the underlying disease and the causation of the effusion was determined.

The diagnostic problems presented by the bilateral effusions were approached in several ways. Neoplastic disease was proved either by a characteristic roentgen appearance, by the examination of excised lymph nodes, the finding of a primary neoplasm elsewhere in the body, or the demonstration of tumor cells in the fluid. Chemical studies aided in the diagnosis of disturbances in electrolyte and water metabolism as a cause of the effusion in some of the cases. Increased protein content, a high specific gravity and pleocytosis of the fluid, and the absence of any elevation in the venous pressure or increased circulation time were also helpful in eliminating the possibility of cardiac failure. This intensified the search for the true cause of the fluid and dyspnea. The cause of the effusions was finally clarified by the clinical course, laboratory findings, and observations of the pathology, either in biopsy specimens, repeated cell blocks of the fluid, or at autopsy.

ETIOLOGY OF THE EFFUSIONS

The causes of the bilateral effusions in our series of 78 cases are classified in Table I. It is notable that in only 3 cases, or less than 4%, could the effusion be ascribed to cardiac failure. The most common cause was neoplastic disease, which was present in almost half of the cases. Furunculosis of the lungs complicating a staphylococcus aureus bacteremia was present in one case. In 2 patients the effusions were due to perforation of the esophagus, and the remaining 37 were divided among patients with polyserositis, metabolic disturbances and pulmonary embolization with infarction.

TABLE 1
Etiology of bilateral pleural effusion in 78 cases

Etiology		Total Cases	Percent of Total
NEOPLASTIC DISEASES			
Metastatic neoplasms	19	35	44.9
Lymphoma	13		
Primary neoplasms	3		
POLYSEROSITIS			
Lupus Erythematosus	4	14	17.9
Tuberculosis	4		
Generalized Adenitis Unknown Etiology	2		
Periarteritis Nodosa	2		
Eosinophilic Pneumonia	1		
Constrictive Pericarditis	1		
DISTURBANCE OF WATER METABOLISM AND ELECTROLYTES			
Nephritis & Amyloidosis	8	13	16.7
Cirrhosis of Liver	3		
Fluid Overloading	2		
PULMONARY EMBOLIZATION			
		10	12.9
PYOGENIC INFECTIONS			
Perforated Esophagus	2	3	3.8
Staphylococcus Sepsis	1		
CONGESTIVE HEART FAILURE			
		3	3.8
Total cases		78	100%

Primary carcinoma of the lung was an unusual cause of the effusions. There were only 3 such cases and the roentgen manifestation in each of them was that of a mediastinal mass. Six of the 13 patients with lymphomatous disease presented evidence of a mediastinal tumor on the roentgen films. The pleural effusions in neoplastic disease of the mediastinum sometimes exhibited the qualities of a transudate as in congestive failure. However, the presence of a mass in the mediastinum established quite definitely that the effusions were not due to this cause. In these cases the effusions were probably due to obstruction of lymphatic flow rather than to neoplastic invasion of the pleura.

The primary origin of the metastatic neoplasms was varied. Carcinoma of the breast was the most frequent cause. The remainder arose from the pancreas, stomach, ovary, kidney, cervix, thymus and bladder. In 5 cases the primary site was not determined but the neoplastic cause was proved either by pathological examination of a lymph node or of a cell block of the fluid.

Of particular interest are the cases of polyserositis which made up about 18% of the series. The table indicates the varied nature of the causes of the polyserositis. In some cases the diagnosis was comparatively simple, whereas in others it was most difficult. In one of them, which was characterized by the presence of large peripheral lymph nodes, the biopsy did not yield information that was sufficiently characteristic for a diagnosis. Only a generalized lymphadenitis of a nonspecific nature was found in another patient who was examined at autopsy.

The patients with disturbances of water metabolism or electrolytes were mostly those in the nephrotic stage of nephritis. The findings were characterized by a hypoproteinemia and an inversion of the albumin-globulin ratio. This was also the case in 2 patients with amyloidosis, and in those with cirrhosis of the liver. One patient in diabetic acidosis, and another with ulcerative colitis, complicated by hypoproteinemia and anemia, developed bilateral pleural effusions as a result of overloading with intravenous saline solution.

The 10 patients with pulmonary embolization presented an interesting group, since some of them were patients with heart disease. They were studied carefully because the heart was of normal size on the roentgen films, and it was established definitely that the effusions were due to pulmonary embolization and not to heart failure.

ASSOCIATED FINDINGS ON THE ROENTGEN FILMS

The presence of additional shadows on the roentgen film was helpful in directing the attention of the roentgenologist to some disease other than cardiac failure as the cause of the effusions in 29 of the cases. In 11 there was evidence of a mediastinal mass. This was present in all of the cases of primary bronchogenic carcinoma, which is rarely associated with a bilateral pleural effusion in the absence of extensive mediastinal involvement. Two of the 19 cases of metastatic carcinoma showed mediastinal masses, while the remaining 6 mediastinal masses were due either to lymphosarcoma or Hodgkin's disease. It was surprising to us to find that only 6 of the 13 cases of lymphosarcoma and Hodgkin's disease had a visible mediastinal tumor in association with the bilateral pleural effusion.

One or more areas of infiltration in the lung were present in 9 cases. Of these, 3 represented areas of pulmonary infarction and 2 were due to metastatic neoplasm. The infiltration was due to eosinophilic pneumonia, periarteritis nodosa, tuberculosis, and furunculosis of the lungs in individual instances. Nodular shadows of varying size occurred in 3 cases of metastatic neoplasm and miliary infiltrations were visualized in one patient with lymphosarcoma without roentgen evidence of involvement of the mediastinal lymph nodes. In 5 instances there were fine, streak-like shadows extending throughout the lungs, representing lymphangitic carcinosis from a primary tumor in a distant organ. It was difficult to differentiate these shadows from those of congestion due to heart failure. However, the small size of the heart suggested the true nature of the shadows to the roentgenologist, and this led to further procedures to prove that the impression gained from the film was correct.

CASES WITHOUT ASSOCIATED ROENTGEN FINDINGS

In the remaining 49 cases, almost two-thirds of the series, there were no shadows in the lungs or mediastinum that might aid in the roentgen diagnosis of the disease underlying the pleural effusion (Table II). No pulmonary or mediastinal lesions could be visualized in 7 of the 10 cases of pulmonary embolization, in 7 of the 19 patients with metastatic neoplasms and in 6 of the 13 cases of Hodgkin's disease or lymphosarcoma. The roentgen evidence of mediastinitis

TABLE II

Associated lesions found in lungs or mediastinum by X ray examination

Diseases	Cases with Shadows	Cases without Shadows
Neoplasms	22	13
Infarcts	3	7
Tuberculosis	1	3
Lung abscesses	1	0
Eosinophilic pneumonia	1	0
Periarteritis nodosa	1	1
Other polyserositis	0	7
Perforated esophagus	0	2
Metabolic disturbances	0	13
Congestive heart failure	0	3
Total	29	49

were obscured by the effusions in both cases of injury to the esophagus. Three of the four patients with bilateral tuberculous pleurisy showed no evidence of pulmonary tuberculosis. Both patients who had a generalized disease of unknown etiology characterized by a polyserositis with diffuse inflammatory disease of the lymph nodes, showed no evidence of enlargement of the nodes on the roentgen films, and 1 of the 2 patients with periarteritis nodosa showed no roentgen evidence of pulmonary involvement.

No abnormalities were noted in the lungs of the patients with a disturbance of water metabolism. The distinctive finding in this group of cases was the absence of clouding of the lungs by thickening of the pleura, pulmonary edema or dilatation of the pulmonary vessels. On the other hand, all 3 patients in whom the effusions were due to cardiac failure showed prominence and widening of the pulmonary blood vessels as a result of the circulatory disturbance.

DIAGNOSIS OF THE CAUSE OF THE EFFUSIONS

In the 29 patients in whom there were roentgen evidences of a mass in the mediastinum or of nodular masses or infiltrations in the lungs it was obvious to the roentgenologist that there was some other cause for the effusions than cardiac failure, and the exact etiology was easily demonstrable from the clinical as well as the roentgen findings. Of the remaining 49 cases with no specific roentgen findings, there were 3 with congestive heart failure. In these three there was dilatation of the pulmonary blood vessels to indicate that there was an impairment in the lesser circulation. In 46 cases, therefore, there was no clue to be derived from the x-ray films as to the nature of the disease which was responsible for the effusions. However, the absence of engorgement of the pulmonary vessels and the normal size of the heart were striking.

In the 7 patients with metastatic carcinoma without visible involvement of the lungs or mediastinum, the diagnosis was confirmed by pathological examination in each instance. This was done either by the demonstration of neoplastic cells in the fluid or the discovery of an enlarged lymph node which was biopsied in 5

of the cases, in one instance at laparotomy, and in the last, only by the findings at postmortem examination. In the 6 cases of Hodgkin's disease and lymphosarcoma, the diagnosis was confirmed by biopsy of a peripheral lymph node.

In the patients with pulmonary infarction there was clear-cut evidence of the diagnosis. Pleural pain, hemoptysis, blood in the fluid and evidences of a phlebitis following an operation furnished proof of the diagnosis. Two of the patients were known to have coronary artery disease, but in these, the presence of a hemorrhagic effusion proved conclusively that the effusions were not due to heart failure.

In the 3 patients with tuberculous pleurisy the diagnosis was made by the finding of tubercle bacilli in the fluid in one, a positive biopsy from the peritoneum in the second, and biopsy of the pericardium in the third. The patient with periarteritis nodosa without pulmonary infiltrations was shown to have this disease by pathological examination of the gall bladder which was removed at laparotomy. The cases of lupus erythematosus were all proved by the finding of the specific cells of this disease in the blood. One patient with polyserositis associated with an unusual form of lymphadenitis had large peripheral lymph nodes and the other was examined at necropsy.

All the patients with renal disease had hypoproteinemia and hypoalbuminemia, and their venous pressures were normal. Similar findings were present in the patients with cirrhosis of the liver. One of the patients with renal disease also had subacute bacterial endocarditis, but again there was no evidence of heart failure. It was also clear that there was no congestive failure in the 2 cases of overloading of the circulation by the intravenous administration of an excess of saline solution. Both these patients had conditions predisposing to transudation, namely, ketosis and hypoproteinemia and anemia.

CASES WITH CARDIAC FAILURE AND A NORMAL-SIZED HEART

Because of the low incidence of bilateral effusion secondary to cardiac failure in patients with a heart of normal size, a summary of the records of the 3 cases is given:

Case 1. A.S., a 54 year old man, experienced severe crushing pain across the chest following unusual physical exertion $2\frac{1}{2}$ weeks before admission. He was admitted to the hospital because of recurrence of the chest pain.

Examination revealed a slightly cyanotic, dyspneic and orthopneic man with dullness at both lung bases. The heart sounds were of poor quality. There was slight bilateral pretibial edema. The laboratory examinations were essentially negative except for a markedly accelerated sedimentation rate. The electrocardiographic findings were pathognomonic of an acute anterior wall infarction.

Examination of the chest at the bedside showed clouding of both lower lung fields probably due to a bilateral effusion, more extensive on the right side. The heart did not appear enlarged.

On bed rest and diuretic therapy the patient improved. The blood pressure varied between 84/56 and 110/62. He was free of pain and his blood pressure gradually rose. The sedimentation rate remained accelerated and after 4 weeks of bed rest he was discharged for convalescence. The patient was readmitted 2 weeks following his discharge from the hospital, complaining of recurrence of the chest pain, palpitation of the heart and slight

respiratory distress. These symptoms responded to bed rest, low salt diet, sedation and limitation of his caloric intake.

At no time was the patient's venous pressure elevated. The circulation time was only 17 seconds, and he was not considered by most observers to be in congestive heart failure. He died suddenly 20 days after discharge from the hospital.

Case 2. J. R., a 51 year old female, entered the hospital with chief complaints of dyspnea and swelling of the ankles of 4 months duration. Until 3 months preceding admission, the patient had no symptoms of cardiac disease and was not known to have hypertension. At that time she noticed orthopnea and shortness of breath on exertion. At the same time her legs began to swell and she suffered from anorexia. She was given digitalis and mercurial diuretics in an irregular fashion. She had a history of mild diabetes of 20 years duration for which she took 10 units regularly every two weeks. However, there had been no recent glycosuria.

Physical examination revealed an elderly woman who was severely orthopneic and cyanotic and had massive anasarca. The blood pressure was 160/105. The fundi showed numerous retinal hemorrhages and tortuosity of the blood vessels. The cervical veins were greatly distended and an hepatojugular reflux was elicited. The breasts and abdominal wall were edematous. There was dullness to percussion and moist rales were heard over both lungs. A systolic murmur was heard, loudest at the pulmonic area. The cardiac rhythm was regular. There was ascites and the legs were edematous.

The hemoglobin was 70%. The urine showed 3 plus albumin and the stool guaiac was 4 plus. The blood urea nitrogen was 25 and the blood sugar was 80 mg.%. The total blood protein was 5.4 g. per 100 cc. The blood Wassermann test was negative. The electrocardiogram showed low voltage of all complexes in all leads. X-ray examination of the chest at the bedside showed a small collection of fluid at the base of each pleural cavity. The pulmonary markings were accentuated, especially on the right. The heart did not appear enlarged.

In spite of vigorous treatment for the heart failure, the patient went progressively downhill and died on the seventh hospital day after an acute episode of pulmonary edema. Permission for a postmortem examination was not obtained. Because of the long history of mild diabetes, relatively recent hypertension, the retinal hemorrhages and the low blood protein, the possibility of a Kimmelstein-Wilson syndrome was considered.

Case 3. R. E., a 46 year old female, entered the hospital complaining of epigastric distress and abdominal distention of 4 months duration. The onset was sudden with postprandial epigastric distress, abdominal distention, constipation and vomiting. The patient had lost 30 pounds in weight during the course of her illness. She had diabetes and she had been taking insulin for 17 years.

Physical examination revealed a well developed and well nourished female in no acute distress. The blood pressure was 160/100. The fundi showed small exudates and punctuate hemorrhages. There were diminished breath sounds and dullness at both lung bases. Rales were present at the right base. There was a soft systolic murmur at the apex of the heart. The liver extended down to the umbilicus and was firm and somewhat nodular. The spleen was enlarged and there was ascites. There was slight edema of the left ankle.

The blood count showed only a mild anemia. There was 2 plus albumin in the urine. The urine was free of sugar. All liver function tests, including the total protein, albumin and globulin levels, were normal. The blood urea nitrogen was 8 and the blood sugar 100 mgs.%. The electrocardiogram indicated myocardial damage. The x-ray examination of the abdomen showed extensive calcification of the splenic and iliac vessels. The kidneys, gall bladder, stomach and colon appeared normal. The x-ray examination of the chest showed a bilateral pleural effusion and slight enlargement of the heart. The pulmonary blood vessels appeared somewhat widened.

The venous pressure was 18 cms. and the circulation time was 18-21 seconds. Two liver aspirations showed nothing of significance.

During the patient's stay at the hospital her liver became larger until it extended 3 cms.

below the umbilicus. Repeated aspirations of the chest revealed yellowish-brown, cloudy fluid containing many non-crenated red blood cells. The specific gravity was 1.012. No tumor cells were seen.

Because of the absence of dyspnea or peripheral edema in the presence of the huge liver and a moderately enlarged spleen, the possibility of cardiac failure was not considered before the 50th hospital day when the venous pressure was found to rise from 18 to 25 cms. on right upper quadrant pressure. Following treatment with digitalis, a salt free diet and diuretic drugs, the patient lost 18 pounds in weight and the venous pressure dropped to 7.5 cms. rising to 11 cms. on right upper quadrant pressure. She was discharged as a diabetic with arteriosclerotic heart disease in cardiac failure, but the clinical findings and the course of her illness were considered most unusual.

DISCUSSION

It is evident from the data that have been presented, that cardiac failure is only rarely the cause of bilateral effusions if the heart is not enlarged. Even the 3 cases that showed evidence of cardiac failure in the presence of a small heart belong to two special categories. One was a patient with an acute coronary thrombosis, and it is well known that pulmonary edema occurs in this condition without enlargement of the heart, particularly when there is a low blood pressure with a shock-like state such as was present in this case. In fact, the clinical impression here was that the patient was not suffering from congestive heart failure and neither the venous pressure nor the circulation time were increased. The other two patients were mild diabetics, under insulin treatment for a long time despite the fact that the blood sugar was low. Both had retinal hemorrhages although the blood pressure was only moderately elevated and there is reason to believe that they were examples of the Kimmelstein-Wilson syndrome. Thus, extraneous factors were present which might have contributed to the occurrence of the effusions. Moreover, in one of the cases the heart was reported as somewhat enlarged, but it was included in the series because the films were not available for review and we did not wish to exclude any case of cardiac failure which could possibly fall within the purview of this study.

There are several cases of cardiac disease in this series, and it is possible that weakness of the myocardium may have contributed to some degree to the formation of the pleural effusions. This may have been the case in some of the patients with polyserositis, in the patient with subacute bacterial endocarditis, nephritis, anemia and hypoproteinemia, and in the two patients with coronary artery disease who suffered pulmonary infarction. However, the determining factor in the production of the effusions was not the disease of the heart, and these cases point up the fact that one must look for other diseases and other factors than cardiac failure to explain the bilateral effusions in the patient whose heart is not enlarged.

The results of this study should be of particular interest and assistance to the roentgenologist. Too frequently he has a tendency to ascribe the effusions to circulatory failure when he is informed by the clinician that the patient is suffering from dyspnea or generalized edema or that the veins in the neck are distended, and the venous pressure in the arms is elevated. If a mass is present in the mediastinum he should dispel the idea of circulatory failure forthwith. Even if no abnormality can be seen on the films aside from the pleural effusions, he should

emphasize the fact that the heart is of normal size and that this makes the possibility of circulatory failure unlikely, and he should urge the clinician to look for some other cause for the effusions.

The search for the underlying cause must be exhaustive. All types of polyserositis must be considered in the differential diagnosis and proper examinations made in an attempt to determine whether a form of polyserositis is responsible for the effusions. Large peripheral nodes should be searched for carefully, and examined pathologically when they are found. Several examinations of the pleural fluid by cell block should be made before excluding the possibility of a neoplasm. In this connection it should be borne in mind that smears may be deceptive. If no other cause for the effusion can be found it may be advisable to induce a pneumothorax followed by roentgen films of the chest with the patient in the lateral decubitus, in a search for neoplastic nodules on the pleura.

No mention has been made concerning chylothorax or of Meigs' syndrome because examples did not occur in this series. However, we have seen bilateral effusions in both of these conditions. The diagnosis is obvious in the case of chylothorax, and can be made by the findings of the pelvic examination and laparotomy in the case of Meigs' syndrome.

SUMMARY AND CONCLUSIONS

1. A series of 78 cases of bilateral pleural effusion without enlargement of the cardiac shadow on the roentgen films was subjected to study.
2. A wide variety of diseases accounted for the effusions.
3. Only 3 cases, or less than 4 %, were due to congestive heart failure.
4. When the roentgenological examination discloses a heart of normal size in a patient with a bilateral effusion, a most careful search is indicated for the cause of the effusions before ascribing them to cardiac failure.

AN AUTOMATIC CASSETTE CHANGER FOR CEREBRAL ANGIOGRAPHY

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Approximately 25 years ago when Egas Moniz was developing the method of study of the cerebral vessels by carotid angiography, he recognized the essential need for a rapid sequence film system which would permit the taking of multiple exposures during the 6-8 seconds which were necessary for the dye to traverse the intracranial vessels. He used a large wheel with cassettes mounted on its periphery, hand operated to bring a new cassette into position beneath the patient's head every second or so.

Nevertheless, as recently as 1949 at The Mount Sinai Hospital, carotid angiography was being performed by as crude a technique as using the standard Bucky table with the technician trying to hand shift a second cassette into place in time to catch the venous end of the circulatory cycle. Several simple pull type changers have been available since that same period which simply use a stack of cassettes with tabs or wires connected to each one to be drawn out manually, pulling the top cassette off each time to allow the next cassette to snap up into position. The x-ray machine would also be tripped manually when the x-ray technician assumed that the new cassette was in the proper place. One such machine was used in Mount Sinai Hospital during 1950. Meanwhile the angiocardiographers at Mount Sinai Hospital had developed a very fine automatic changer system which dropped the cassette through at high speed with automatic triggering of the x-ray machine, and did very satisfactory angiocardiographic studies. At about this same time there became available the various roll film sequence x-ray cameras in which a continuous roll of film was rapidly advanced between two intensifying screens which were then clamped together for the instant of the exposure and released again with the next advance.

We felt that none of these systems was completely satisfactory. The hand pulled changer had a disadvantage of inadequate timing of the synchronization of the cassette pull and the x-ray trigger, and an inadequate number of films. It had the advantages of using the standard cassettes and regular developing methods, and of being inexpensive. The roll film system also had several disadvantages, the most serious one being that we felt that continuously good sharp detail was unobtainable. This appeared to be because the procedure of releasing the intensifying screens and then reclamping for each exposure did not seem to consistently produce exacting pressure plate apposition of the screens to the film, thereby producing a blur in the pictures. There was a considerable delay in processing the film, generally making it impractical to have each sequence seen before the next injection. In addition, the roll film system was relatively expensive. It was, therefore, decided that a completely automatic cassette changer should be built and that this changer should use standard x-ray cassettes. A se-

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quence of 7 films was decided upon as providing all needed information and as much exposure as we cared to give in an individual x-ray examination. We decided that the films should be able to be taken at one second intervals or longer and that the cassette changer should automatically trip the succeeding x-ray exposures.

A changer which was designed to these specifications has now been in use at The Mount Sinai Hospital for the past 5 years and has been used for more than 10,000 film exposures. The quality of the x-rays taken is as high as that of the plain skull film taken on the grid cassette under the best conditions.

The machine itself consists of a welded steel frame mounted on heavy casters and is roughly triangular in shape. It was decided to make the taking area on a 45 degree angle with the horizontal. By so doing, the patient could be positioned in a 45 degree angle trough so that AP and lateral views could be taken without rotating the head merely by placing the machine under either the left or the right side of the angle trough. This is shown in Fig. 1A where the unit is being used to take an anterior-posterior projection. Simply by pushing the machine around under the other side of the head and shifting the x-ray tube, the lateral projection will be taken (Figure 1B). By so doing, the rotation of the patient's neck is avoided. It also becomes unnecessary to mount the changer on a very heavy and expensive tilt mechanism, or to make the cassette changer in duplicate with separate sections for AP and lateral views.

In fig. 1C the lead rubber protective shield is shown in place. This is put into position as soon as the artery has been cannulated. With the proper X-ray cone and the shield in use the total radiation to the operator has been measured as well under 1 milliroentgen per exposure.

In the center of the changer (Fig. 2) is a spring loaded plunger which is balanced to carry the weight of 7 cassettes, and as each cassette is pushed off the top of the stack, the remainder of the stack is lifted by the plunger into virtual contact with the overlying Lysholm grid. The cassettes are pushed off the stack by a pusher riding in bearing protected channels of machined steel. The pusher is somewhat thinner than one cassette and is forced against the inferior edge of the upper cassette by an eccentric mounted on the drive system. The pusher forces the cassette off the top of the stack throwing it upward into the receiving compartment at the top of the machine where the exposed cassettes are collected (Fig. 5D). The drive system which provides the power for the pusher consists of a $\frac{1}{4}$ horsepower motor geared down to 128 revolutions per minute. In use, the motor runs continuously from the time the machine is first alerted. The gear system of the motor is coupled to the pusher shaft through a clutch mechanism which was designed to operate as a one-shot system. A release plunger on the bottom of the clutch system is electrically operated by a solenoid permitting the clutch to engage. The clutch engages for one full revolution whereupon it automatically throws out of gear and locks to prevent further rotation or roll back, until the solenoid is triggered again, repeating the cycle.

A simple motor driven timer was considered far more reliable and less expensive for this particular application than an electronic timer and requires no warm-up time or checking for future accuracy. The timer is shown in Fig 3.



FIG. 1. A: Cassette changer set up for AP projection with right carotid injection. B: The changer has now been moved to take the Lateral views with right carotid injection. C: Lead rubber protective screen in place to shield operator.

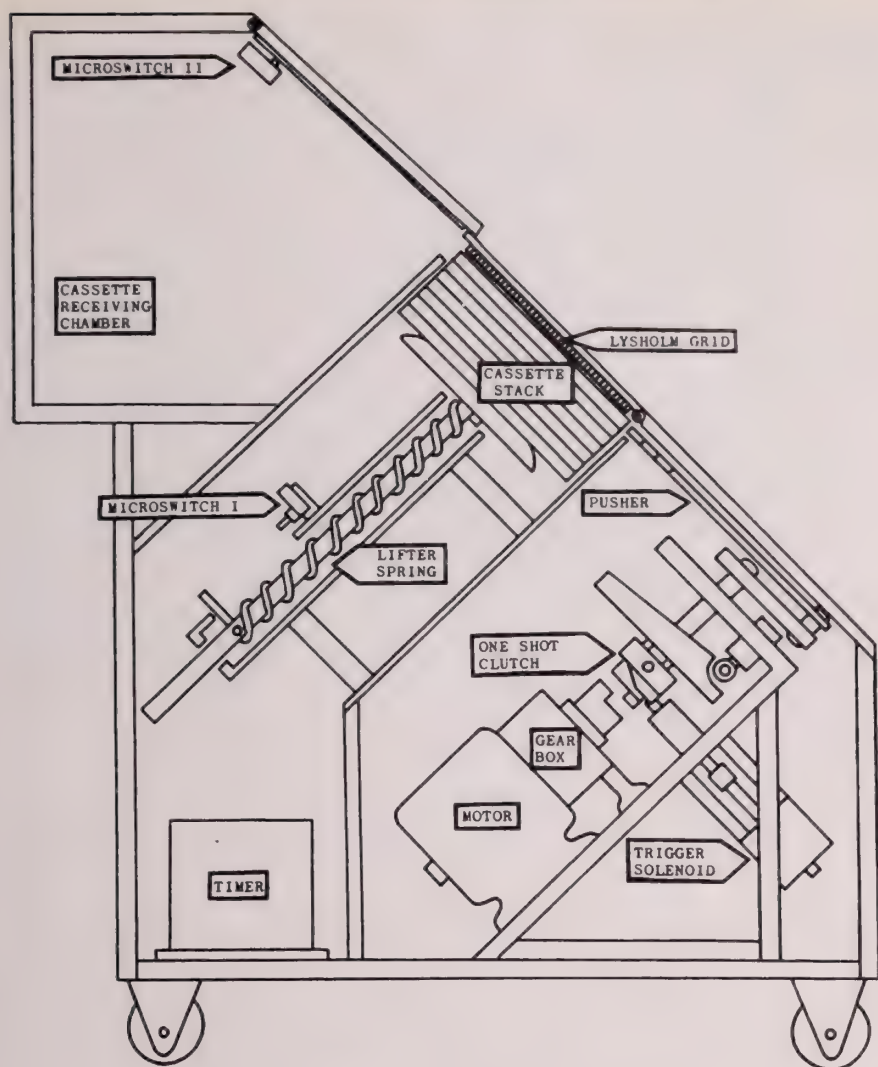


FIG. 2. Diagram of construction of changer.

and consists of a Holzer-Cabot timing motor, driving an aluminum drum which was geared to operate at one revolution every 8 seconds. Three microswitches were mounted so that their roller actuators rolled on the drum. By placement of tapped holes on the surface of the drum ordinary machine screws could be put into the drum to trip the microswitches in appropriate sequence. Microswitch III continues the rotation of the drum after the initial starting of the unit for the full 8 seconds of a rotation. Microswitch IV is normally closed when in position on the drum and is opened when it hits the protruding screws. This interrupts the x-ray trigger so that the x-ray timer which is used for the actual timing of the x-ray exposure will be able to recycle. In this way the x-ray exposure is not limited by the length of time that the roller is on the actuator but

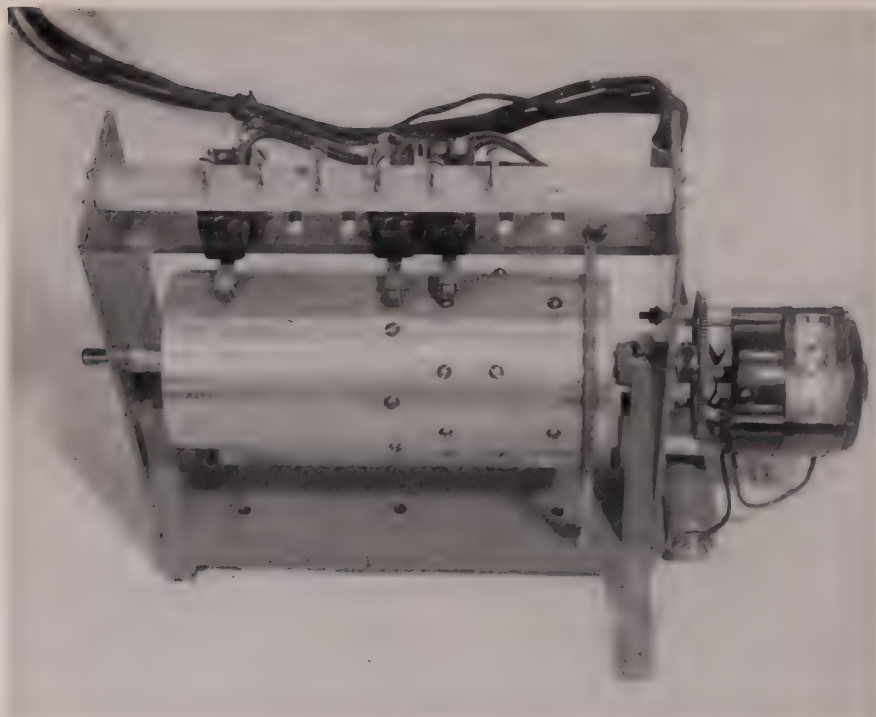


FIG. 3. Timer unit.

is triggered as soon as the roller drops off the screw, and will remain on until cut off by the automatic x-ray timer of the x-ray machine. Microswitch V triggers the starter solenoid which operates the one shot clutch on the motor drive system. The electrical circuit is shown in Fig. 4.

The sequence of operation of the machine is initiated by turning on the main power switch to the changer. This closes the relay which starts the motor of the cassette changer and also begins the rotation of the anode of the main x-ray tube. When the injection is being made into the carotid the start trigger button is then pressed and released. The timer at once begins to run and the first x-ray exposure begins instantly with the touching of the starter switch. Half a second later the cassette is shifted, the new cassette comes into position, a process taking approximately 0.4 second. One tenth of a second later the next x-ray exposure begins. Our present x-ray exposures have been between 0.1 second and 0.3 second. Vibration in the cassette changer has been minimized by the extremely solid construction and its heavy weight has not been a disadvantage in ordinary use. It simply rolled from one side of the patient to the other side once during the course of the arteriogram. The changer is always used with the same x-ray machine into which the various cable connections have been made to permit the cassette changer relay to trigger the rotating anode and the cassette changer timer to trigger the start of exposures.

Several safety devices have been incorporated. It was felt, for example, that

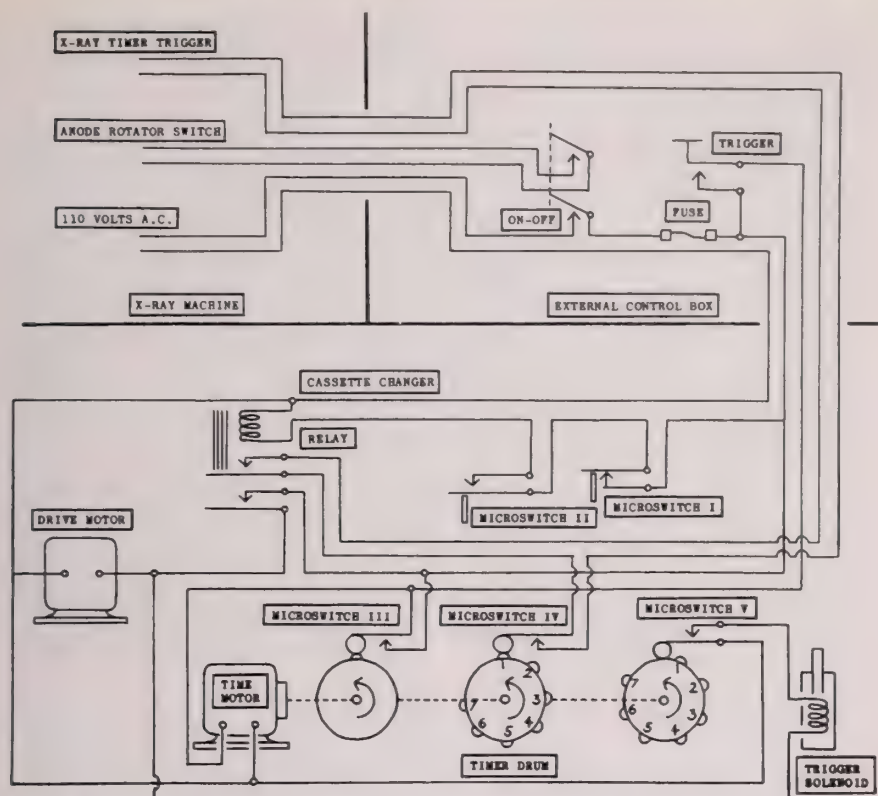


FIG. 4. Wiring diagram of changer, timer, control box and connections to X-ray machine.

the machine should automatically disable itself if the lid were lifted during operation. This is accomplished by the switch (microswitch II) which interrupts through the relay the power to the main drive motor and the x-ray trigger. Also on the cassette holding stack there is a cut off switch (microswitch I) which will interrupt the same relay as soon as there are no more cassettes left in the stack. This permits the insertion of any number of cassettes less than the 7 which constitute a full load with the machine stopping as soon as the cassettes have been used. With this method, as a matter of fact, it is our custom to take a scout film of the skull by loading only a single cassette, whereupon the machine will shift that cassette out of position and turn itself off. We usually then develop that film to check upon our exposure density for this particular patient during the interval while the patient is being prepared and the carotid is being needed. The film can then be inspected and any necessary exposure correction made before the actual angiographic films are taken. The machine is loaded completely after the single scout film is taken. To load the changer, the cassette lifter is pressed down a short distance and each cassette slid in successively, one above the other (Fig. 5: A, B, & C).

The cassettes used in the changer were purchased new as a group to assure

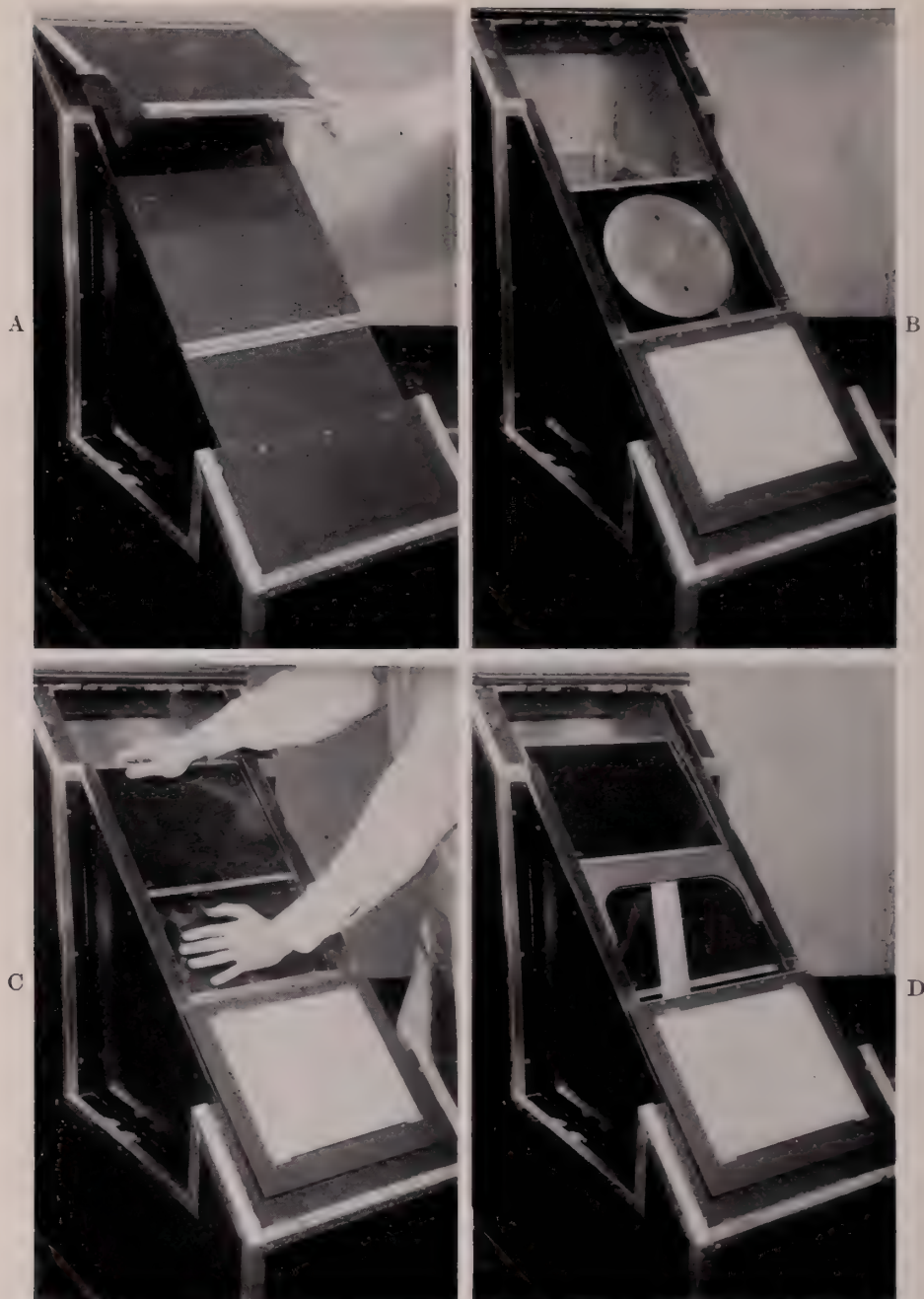


FIG. 5. A: Cassette receiving chamber lid being lifted. B: Lysholm grid hinged down to show cassette lifter. C: Loading the changer. D: Pusher extruding a cassette. In actual operation the lids would have to be closed.

uniformity and are kept separately for this purpose. They have been slightly modified by the installation of a lead sheet 0.5 mm. in thickness inside each of the cassette backs underneath the intensifying screens.

The patient is placed upon an old modified operating table of light construction to which has been added a V-shaped trough with radiolucent sides which are perpendicular to each other and 45° from the horizontal. This trough extends from the end of the table, and carries the head of the patient, as shown in Fig. 1. The patient is placed on the stretcher with the head rotated so that the sagittal plane is parallel to one side of the trough, with the side to be injected upward.

The injection of the carotid artery is almost invariably done percutaneously. Our present technique is to inject 10 cc of 50% Hypaque completing the injection in approximately one second. The machine is triggered about halfway through the injection. Serial films then show early arterial, arterial, late arterial and precapillary, capillary and venous phases.

Use of this automatic changer has considerably aided in accurate localization of brain tumors, vascular lesions, and such sequelae of trauma as subdural hematoma, and has permitted research studies of the cerebral vascular system which would not have been possible without an accurate automatic serialograph.

ACKNOWLEDGMENT

The author would like to thank Dr. Sergei Feitelberg, Director of the Andre Meyer Department of Physics, and Dr. Bernard S. Wolf, Director of the Department of Radiology, of The Mount Sinai Hospital, for their helpful advice in the design of this machine. I would also like to acknowledge the contribution of Mr. Gus Ogren, machinist of the Department of Psychology of the Yale University Medical School, who carried out the basic machine work in the construction of this unit. Finally, I should like to gratefully acknowledge the preparation of the illustrations by Mrs. Mynell Smollett.

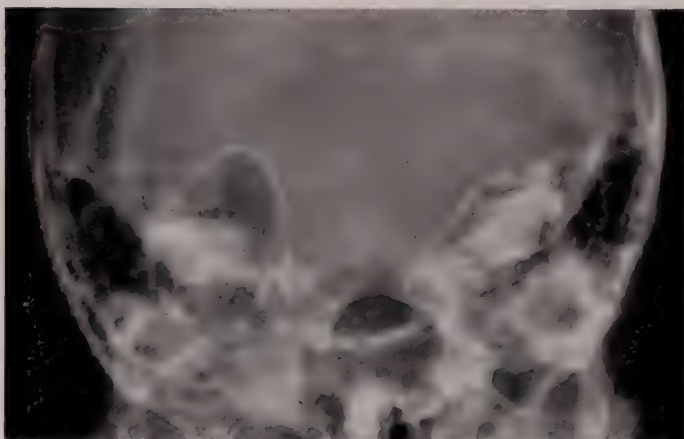
Radiological Notes

ROENTGEN FEATURES OF UNUSUAL CASES

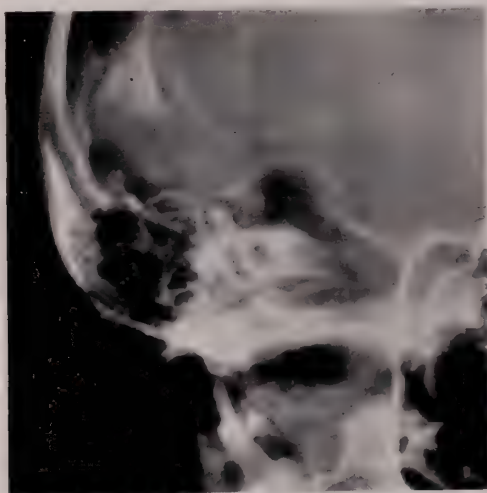
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New York, N. Y.

CASE NO. 1



CASE 1, FIG. 1 Towne-Twining view of petrous pyramids. Marked protuberance of the medial portion of the right petrous pyramid.



CASE 1, FIG. 2 Stenvers view of the right petrous pyramid showed similar findings.

A 35 year old male presented himself with the chief complaints of right frontal headaches, pain and numbness of the right side of his face, blurring of vision and diplopia. Neurological examination showed trigeminal sensory loss and a mild peripheral facial palsy on the right side.

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Roentgen examination of the skull (Fig. 1, 2) showed a remarkable protuberance of the medial portion of the right petrous pyramid. The bony cortex over this region was intact and the area was radiolucent. On detailed inspection, a band of soft tissue density about $\frac{1}{8}$ inch in width could be seen immediately underneath and parallel to the intact cortex.

Posterior fossa exploration was performed after a pneumoencephalogram demonstrated elevation of the temporal horn overlying the petrous pyramid. It was demonstrated that the bulging area in the petrous pyramid was a huge air cell.

Final diagnosis: HUGE AIR CELL IN THE TIP OF THE PETROUS PYRAMID; A DEVELOPMENTAL ANOMALY.

CASE NO. 2



CASE 2, FIG. 1 Spot films of the distal esophagus showing a beaded appearance suggesting esophageal varices. Fluid barium mixture was used.

A 50 year old male with a history of considerable alcoholic intake was admitted because of massive hematemesis. A Sengstaken-Blakemore tube did not control the bleeding despite the application of tension on the tube. An emergency barium swallow was requested for the demonstration of esophageal varices.

Roentgen examination showed multiple small circular defects suggesting a row of beads separated by circuitous linear collections of barium throughout the lower third of the esophagus (Fig. 1, 2). The appearance was interpreted as



CASE 2, FIG. 2 Film of the distal esophagus during swallowing of fluid barium with findings similar to Fig. 1.

confirmation of the clinical impression of esophageal varices. The patient did very poorly and succumbed about 36 hours after admission. At autopsy, no varices were found. Instead, the esophagus showed a very severe erosive and hemorrhagic esophagitis with alternating longitudinal ulcerations and islands of residual edematous mucosa. The cause of bleeding was a benign gastric ulcer at the cardia which showed an arteriosclerotic vessel in its base.

In retrospect, it was pointed out that the diagnosis of esophageal varices might have been avoided if the lack of distensibility of the involved area had been realized. In the presence of varices, distensibility is usually increased. The gastric ulcer seen at autopsy could not be identified on review of the films.

Final diagnosis: ACUTE EROSIVE AND HEMORRHAGIC ESOPHAGITIS ASSOCIATED WITH AN INDWELLING SENGSTAKEN-BLAKEMORE TUBE.



FIG. 1

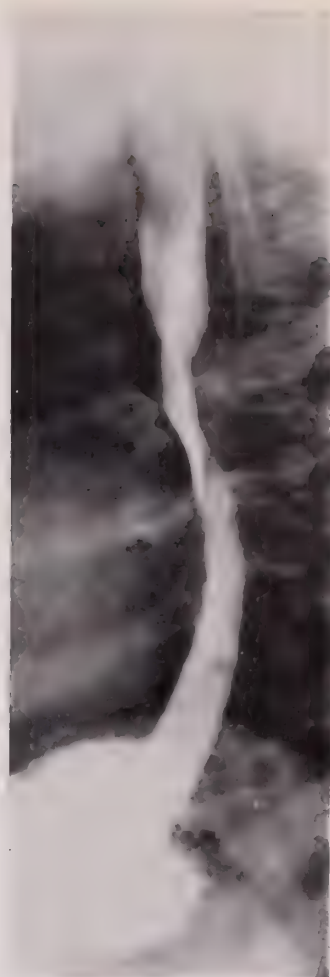


FIG. 2

CASE 3, FIG. 1 Prone right anterior oblique view of the esophagus. Shows 5 equally spaced discrete indentations on the right posterolateral wall of the esophagus.

CASE 3, FIG. 2 Left anterior oblique view of esophagus shows a shallow elongated impression on the posterior wall of the esophagus below the level of the carina.



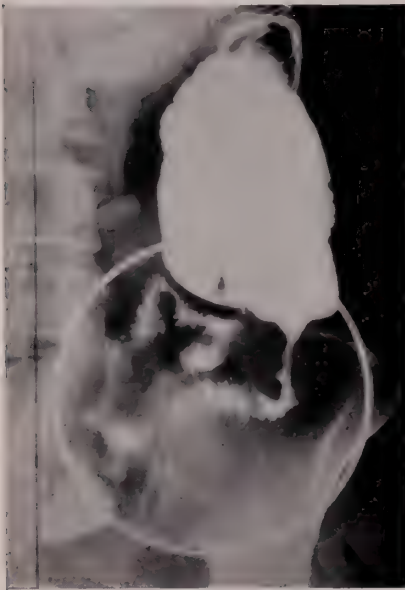
CASE 3, FIG. 3 Conventional P-A chest film.

This was a young adult in whom examination of the esophagus in the prone right anterior oblique projection showed at least five discrete indentations on the right posterolateral wall of the esophagus (Fig. 1). These were seen only with optimum filling of the esophagus and did not appear to extend around the wall for any great distance. These indentations were not visible in the left anterior oblique position (Fig. 2). In this latter projection, a rather diffuse shallow impression was seen on the posterior wall of the esophagus below the carina.

The diagnosis in this case was known clinically and could easily be determined from the conventional P-A film of the chest (Fig. 3). The heart was enlarged, the ascending aorta dilated, the left subclavian artery prominent and the upper ribs showed notching typical of coarctation of the aorta. The grooves on the right posterolateral wall of the esophagus therefore represent "notching of the esophagus" as result of pressure by dilated anastomatic intercostal arteries crossing between the esophagus and the spine to join the descending aorta to the left of the midline. The posterior indentation seen in the left oblique view is the result of pressure due to post-stenotic dilatation of the aorta distal to the site of coarctation.

Final Diagnosis: NOTCHING OF THE ESOPHAGUS ASSOCIATED WITH COARCTATION OF THE AORTA.

CASES NO. 4, 5, 6



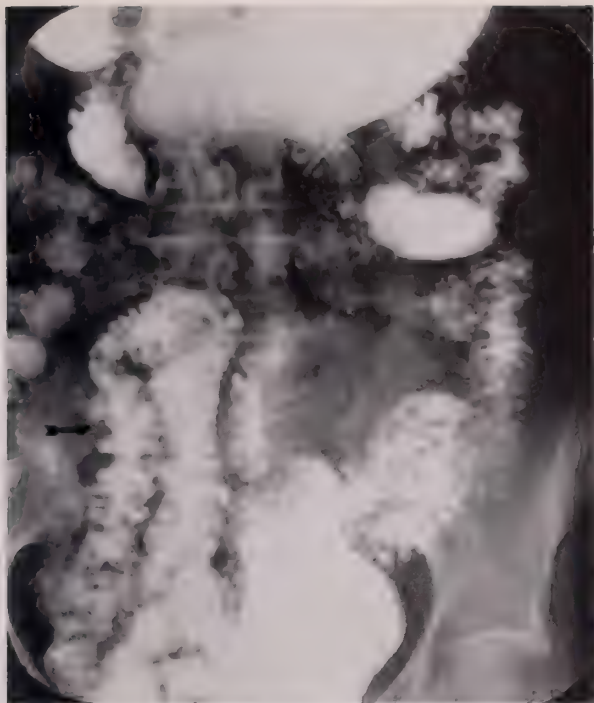
CASE 4, FIG. 1



CASE 5, FIG. 2

CASE 4, FIG. 1 Obstructive jejunal lesion. The opaque circle is an artifact due to the use of a compression balloon.

CASE 5, FIG. 2 A non-obstructive jejunal lesion resembling Case No. 4.



CASE 6, FIG. 3 The upper arrow shows another jejunal lesion resembling Cases No. 4 and No. 5. There is, in addition, evidence of an extrinsic mass pressing on this and the more distal loop. The lower arrow indicates another shorter lesion of the same type.

Three different patients showed discrete small bowel lesions on roentgen examination. Case No. 4, Fig. 1 shows a segment of jejunum about $1\frac{1}{2}$ inches in length which is markedly narrowed, straightened with scalloped margins and effaced mucosal pattern. No "overhanging edges" are seen either proximally or distally. Proximally, there is a short funnel shaped segment which joins dilated bowel. Distally, there is an abrupt transition to normal mucosal pattern. An adjacent loop of bowel located medially remains at an unusually great distance from the involved segment.

Case No. 5, Fig. 2 shows a lesion of the jejunum with many of the features seen in Case No. 4. The involved segment is not markedly narrowed and there is no dilatation proximal to it; i.e., there is no evidence of obstruction. The contours of the involved segment are coarsely scalloped with eccentric involvement proximally and distally. The loops of bowel adjacent to the involved area remain unusually far from it, but in general appear to parallel it.

Case No. 6, Fig. 3 shows a somewhat arcuate segment (upper arrow) which was not normally distensible with thickened or very coarse mucosal pattern. The curvilinear configuration of this segment associated with displacement of the adjacent loops of bowel suggests presence of a somewhat globular mass which also flattens the left aspect of the loop distal to the narrowed segment.

There is no distinct proximal or distal demarcation to the narrowed area. The lower arrow in Fig. 3 shows another short segment which is not narrowed but in which the normal valvulae appear thick and diminished in number.

The descriptions of the roentgen findings in these three cases are inadequate to express the "family resemblance" which is obvious when the films are placed next to each other.

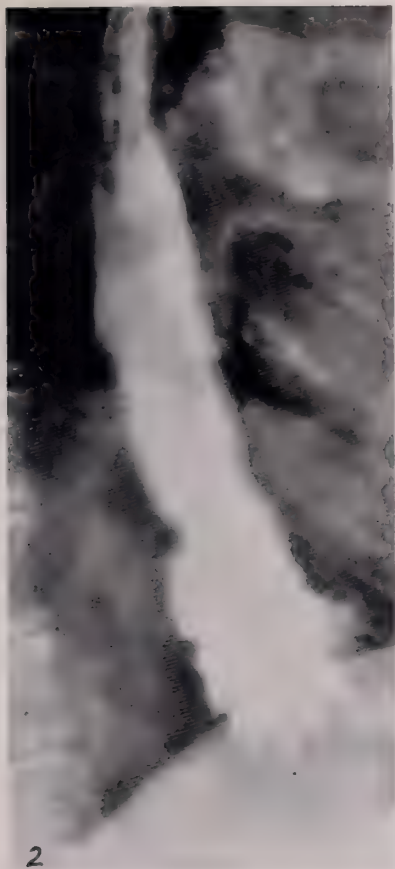
Final diagnosis: HODGKINS DISEASE OF THE SMALL BOWEL.

CASE NO. 7



CASE 7, FIG. 1 A filled esophagus shows a small hiatus hernia of the "short esophagus type" with a ragged margin of the esophagus for a considerable distance above the hernial sac.

This is a female about 50 with symptoms attributed to a hiatus hernia. Examination of the esophagus confirmed the presence of a small "short esophagus type" of hiatus hernia with apparently intact mucosal pattern within it. However, (Fig. 1, 2, 3) the contour of the filled esophagus above the hernial sac showed a ragged outline which was most marked posteriorly. There was no



2

CASE 7, FIG. 2



3

CASE 7, FIG. 3

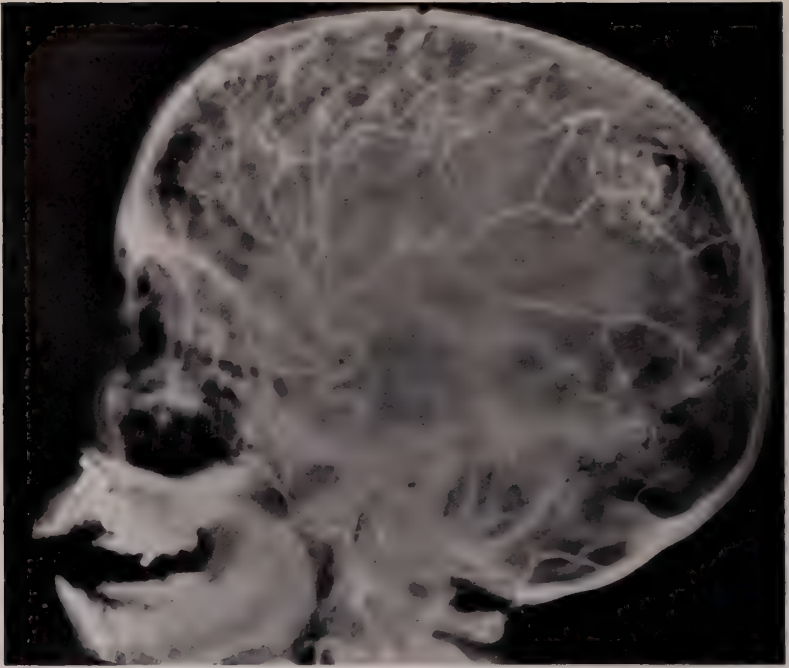
CASE 7, FIG. 2 Findings similar to Fig. 1.

CASE 7, FIG. 3 Filled esophagus with patient erect. The indentation of the barium column posteriorly above the diaphragm was not constant.

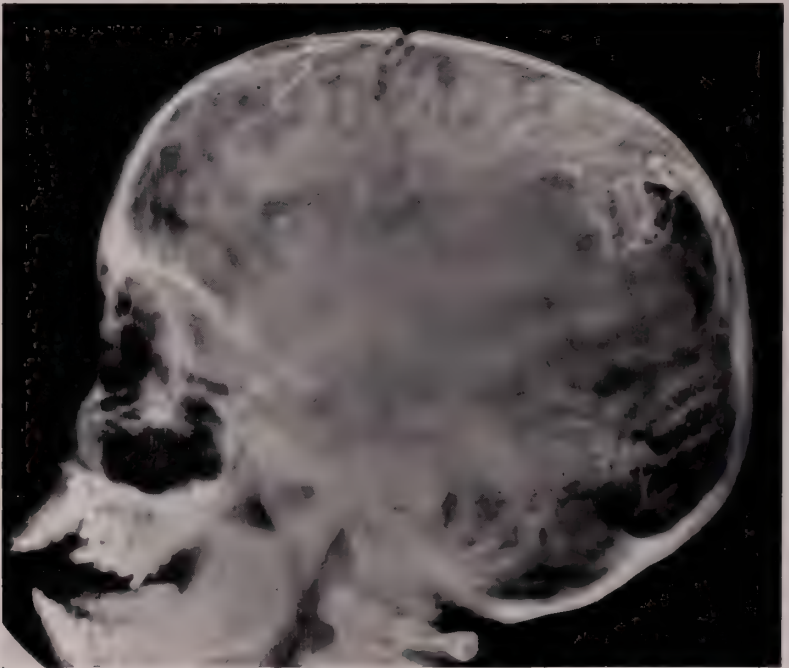
limitation of distensibility, no apparent ulceration, no filling defect and no remarkable spastic phenomena.

The diagnoses of peptic esophagitis and hiatus hernia were made. At thoracotomy, however, there was a suspicious thickening of the esophagogastric region and an esophagogastric resection was performed. On opening the specimen, its appearance seemed relatively normal with intact mucosa. However, on microscopic section, a thin layer of adenocarcinoma cells was seen extending throughout the mucosa of the stomach and the esophagus. Incidentally, this patient returned about one year later, still in relatively good general health and without dysphagia. The examination at that time again showed minimal findings at the anastomotic site, but biopsy esophagoscopy again showed a thin layer of carcinoma in the mucosa.

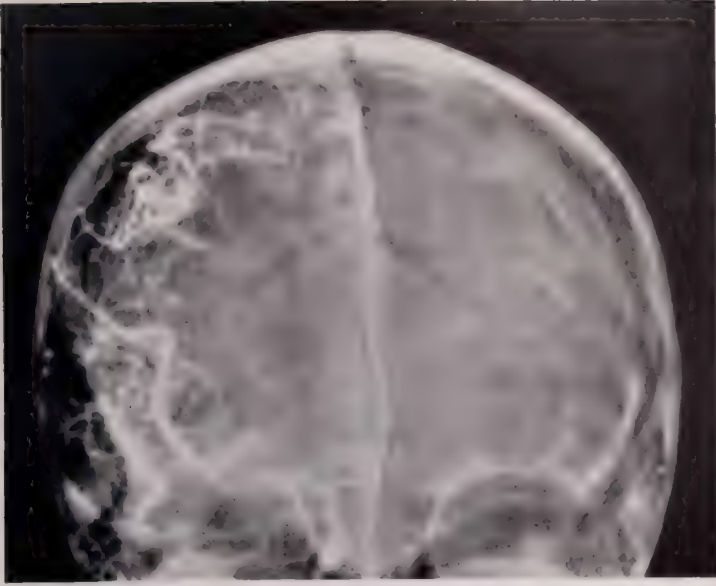
Final diagnosis: SUPERFICIAL SPREADING CARCINOMA, PRIMARY IN THE STOMACH AND EXTENDING INTO THE ESOPHAGUS.



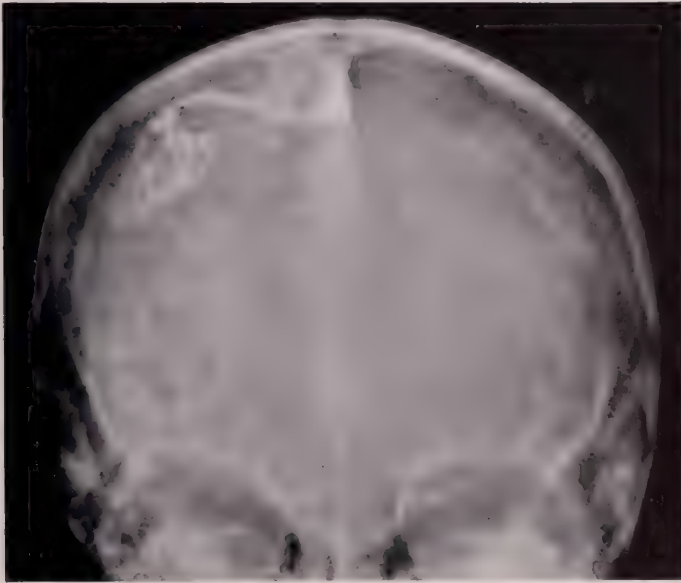
CASE 8, FIG. 1 Right percutaneous carotid angiography, lateral projection, shows elevation of the middle cerebral vessels in the Sylvian fissure with remarkable straightening and spreading apart of the parietal and temporal branches. The parietal branch is unusually wide and supplies knot of tortuous vessels located peripherally. There is simultaneous filling of cortical veins extending to the superior sagittal sinus.



CASE 8, FIG. 2 "Capillary phase" shows persistent filling of the localized collection of vessels in the parietal region.



CASE 8, FIG. 3 The A-P projection confirms the previous findings and demonstrates slight displacement of the anterior cerebral artery to the opposite side.



CASE 8, FIG. 4 "Capillary phase" in the A-P projection with findings similar to Fig. 2.

This is a 10 year old child who was admitted with evidence of an expanding intracranial lesion on the right side.

Percutaneous right carotid arteriogram was done in both the lateral (Fig. 1, 2) and A-P (Fig. 3, 4) projections. These showed elevation of the middle cerebral

vessels in the Sylvian fissure with marked separation of unusually long parietal and temporal branches over the mid and posterior portions of the hemisphere. The parietal branch was unusually wide and supplied a localized collection of tortuous interlacing vessels, both arterial and venous, located superficially in the parietal region about 2 inches from the midline. Large cortical veins draining this area were promptly filled and seen to extend to the superior sagittal sinus. In the A-P projection, there was slight displacement of the anterior cerebral artery to the opposite side.

The lesion visualized on arteriography appeared to consist of two components, 1—a large area in the parietotemporal region in which the vessels were straightened and spread apart, but in which there was no evidence of tumor vascularization and, 2—a knot of tumor vessels superficially located and in relation to the superior and lateral aspects of the larger involved area. The diagnosis of a large cystic lesion with a vascular mural nodule, as seen in an hemangioblastoma, was suggested and confirmed at craniotomy.

It is of note that, while this type of lesion is common in the cerebellum, its occurrence in the cerebral hemisphere is quite rare. The prognosis in general is good.

Final diagnosis: HEMANGIOBLASTOMA OF THE CEREBRAL HEMISPHERE IN A 10 YEAR OLD CHILD.

CASE No. 1	HUGE AIR CELL IN TIP OF PETROUS PYRAMID
CASE No. 2	ACUTE EROSIVE AND HEMORRHAGIC ESOPHAGITIS WITH THE USE OF AN INDWELLING SENGSTAKEN-BLAKEMORE TUBE
CASE No. 3	NOTCHING OF THE ESOPHAGUS ASSOCIATED WITH COARCTATION OF THE AORTA
CASES No. 4, 5, 6	HODGKINS DISEASE OF THE SMALL BOWEL
CASE No. 7	SUPERFICIAL SPREADING CARCINOMA, PRIMARY IN STOMACH AND EXTENDING INTO THE ESOPHAGUS
CASE No. 8	HEMANGIOBLASTOMA OF THE CEREBRAL HEMISPHERE IN A TEN YEAR OLD CHILD

COMPRESSION DEVICE FOR INTRAVENOUS UROGRAPHY

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Compression of the ureters is an accepted technique to produce complete filling of the pelvis and calyces of the kidneys during intravenous urography. Most of the methods presently in use utilize a compression band which immobilizes the patient as well as producing pressure on the abdomen over a rather large area. A rather simple device has been developed on the continent and has been used at this hospital for some time with considerable success (Fig. 1). The



FIG. 1. The device consists of two cone-shaped, hollow plastic molds mounted on a resilient piece of wood joined on each side to a canvas band by belts.

advantages of this device are that a patient may be rotated into the oblique positions without releasing pressure since counterpressure is made by a belt surrounding the patient. Moreover, the pressure on the abdomen is localized to two small areas and is better tolerated by the patient. The fact that the normal lumbar lordosis is maintained also assists in producing ureteral compression. The pressure cones are radiolucent and made out of plastic material so that confusing shadows are avoided. Figures 2 and 3 show the well filled pelvis and calyces with the pressure device in place and complete filling of the ureters immediately after the device is removed.

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FIG. 2. Example of pyelogram taken with compression.



FIG. 3. Film taken immediately after removal of the device shows filling of the ureters throughout their extent.

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A METHOD OF ANALYZING ELECTROCARDIAC ENTITIES IN SPACE

I: THE ORTHOVECTORCARDIOGRAM, A REPRESENTATION OF MAGNITUDE AND ORIENTATION OF THE INSTANTANEOUS FORCES OF THE CARDIAC CYCLE

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Vectorcardiography is based on the premise that the electric field of the heart affects body surface electrodes as though it originated from a relatively small source of dipole current within a homogeneous conducting medium. There is evidence to support this view (1-7), and the following presentation is based on the assumption that it is valid.

The electromotive force of the heart at any instant may be represented as a vector peculiar to that instant. This has a magnitude, a direction, and a sense (polarity) and is symbolized by an arrow. The vector is visualized by the spatial relationship between its terminus and its origin, the null-point. Two symbolic points therefore delineate the resultant electromotive force at a given moment. During the cardiac cycle, one of these, the null-point remains fixed. The other, the terminus, performs a series of convolutions which trace three, successive loops in space, P, QRS, and T.

It is the study of these loops, the implications of their configurations, rates and rhythm of inscription, with which electrocardiography is concerned. The years between the development of the galvanometer and the clinical application of the oscilloscope have been charged with a massive weight of research and the accumulation of a wealth of diagnostic criteria based on linear leads. Twelve are generally employed today. These probe the loops, each tracing a derivative of spatial forces on its own axis. The introduction of clinical vectorcardiography and the oscillographic recording of projections of the loops on the cardinal planes is a closer approach to the source, the spatial vector, and has stimulated a formulation of criteria based on such projections (8-18).

There are three cardinal planes: the frontal (F), the horizontal (H), and the sagittal (S). There are three cardinal directions: the transverse, X, (side-to-side), the vertical, Y, (up-down), and the sagittal, Z, (back-forth). The position of a point in space, here the vector terminus, is determined in reference to these planes and axes.

In fig. I, the convolutions of a complete cardiac cycle and its projections on the cardinal planes are depicted. This is a hypothetical case of left bundle-branch block (8). The spatial loops are shown as ribbons emanating from a null-point. The instantaneous resultant forces at 0.01 second intervals are indicated by dots, some of which have been omitted from the P and T loops to avoid complexity. These represent the termini of successive vectors originating at the null-point.

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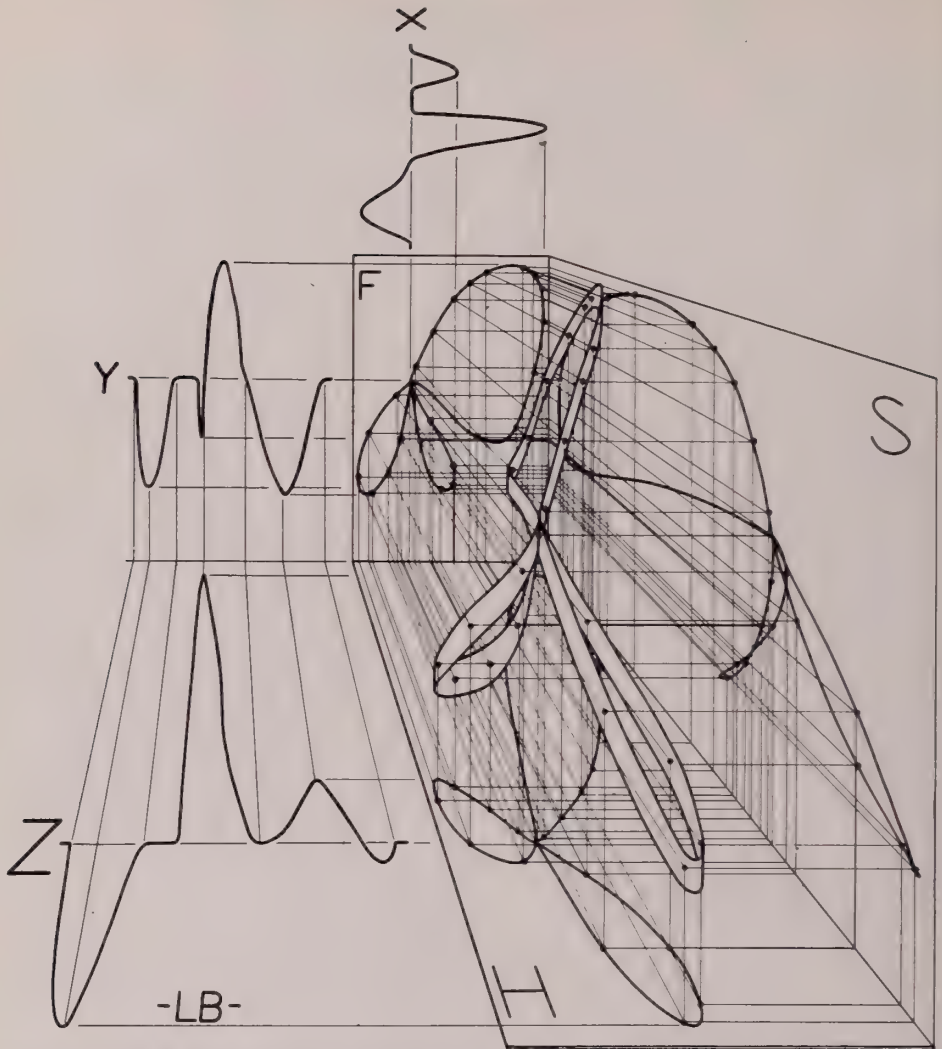


FIG. 1. The P, QRS, and T loops of a hypothetical case of left bundle-branch block are shown as ribbons emanating from a nullpoint. The dots represent the termini of successive vectors. Each terminus has three Cartesian coordinates, X, Y, and Z. These plotted in sequence trace the X, Y, Z curves. At any instant, the frontal projection is the resultant of X and Y; the horizontal, of X and Z; the sagittal, of Y and Z.

The linear curves, X, Y, and Z, are their rectilinear, or Cartesian, coordinates integrated with time. The projections yield more information. Each presents the magnitude and orientation of the spatial vector as projected to its corresponding plane. At each instant the frontal projection is the resultant of the X and Y components; the horizontal, of the X and Z; the sagittal, of the Y and Z. Projections have been employed to explain linear tracings, but this is not their purpose. It is rather to describe the spatial loops, the source of all linear and planar patterns. This they do, but incompletely.

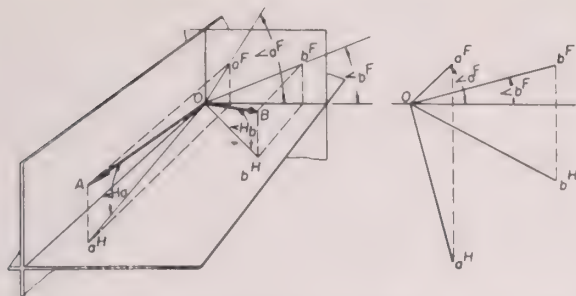


FIG. 2. Two vectors, OA and OB, are shown pictorially and orthographically. They are of equal length and subtend identical angles with the horizontal plane ($<H_a$ and $<H_b$). Their projections on the frontal plane (Oa^F and Ob^F), however, and their axes on this plane ($<a^F$ and $<b^F$) differ widely from the spatial values and from each other.

In fig. 2, vectors OA and OB are equal in magnitude and subtend equal angles with the horizontal plane ($<H_a$ and $<H_b$). As projected to the frontal plane, however, the magnitudes (Oa^F and Ob^F) and angles ($<a^F$ and $<b^F$) differ widely from the spatial values and from each other. In fact, the projection of magnitude may vary from zero to its true length; the projection of the angle, from its true size to 90° . Simple observation of the individual projections is therefore misleading. True magnitude and orientation in space can, however, be determined. In two recent studies a method was advanced of extracting this information from the projections (19, 20). If we return to fig. 2, we note that as the vector approaches the frontal plane, the projections of its magnitude and angle with H more closely resemble the spatial values. If it were therefore completely rotated into F, these would be inscribed on F. This can be performed orthographically.

The full potentialities of orthographic projection have not been realized. It is the method *par excellence* for the analysis of spatial forces. It is an aid to visualization and offers a simple means for the rapid solution of problems that present untold difficulty to the mathematician. The procedure to be described involves no computations and may be performed by rote. As it is dependent, however, on the utilization of a single surface for the recording and visualization of spatial entities, a knowledge of the basic principles by which this is achieved is necessary for a proper understanding of the method. These shall therefore be briefly reviewed.

In orthographic analysis the horizontal and frontal planes are considered transparent and intersect at a ground-line (GL). By their intersection they form four dihedral angles, or quadrants, as in fig. 3a.

The first (I) is above the horizontal and anterior to the frontal plane.

The second (II) is above the horizontal and behind the frontal.

The third (III) is below the horizontal and behind the frontal.

The fourth (IV) is below the horizontal and anterior to the frontal.

These are further split into (subject's) right and left halves by a profile, or sagittal plane, so that space is subdivided into octants labelled IL, IR, IIL, etc. The observer is always stationed in I.

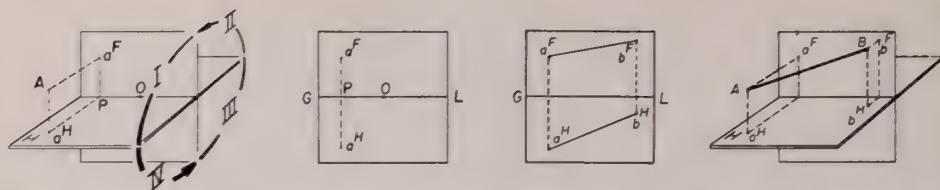


FIG. 3a. The horizontal and frontal planes intersect at the ground-line and divide space into four quadrants. The projection of a point on a plane lies at the foot of a perpendicular (projector) from the point to the plane. a^F and a^H are the respective frontal and horizontal projections of point A. To represent these on a single surface, the horizontal plane is rotated about the ground-line until it is superimposed on the frontal plane, the anterior portion moving down, the posterior up. Fig. 3b. Orthographic representation of point A. a^H has been brought below the ground-line (GL). The interrupted line of recall connects the projections, is perpendicular to GL, and intersects it at P. OP , Pa^F , and Pa^H are the Cartesian, or XYZ, coordinates of point A. Fig. 3c. Orthographic representation of line AB. Fig. 3d. Pictorial representation of AB.

A point in space is represented by its projections on the H and F planes. Each projection lies at the foot of a perpendicular from the point to its respective plane. In fig. 3a, a^H and a^F are the respective H and F projections of point A.

To represent A on a single surface, the H plane is rotated about GL until it coincides with the F plane, the portion of H anterior to GL falling down, and that posterior to GL moving up. In this new position, all of the plane of the paper above GL represents that part of the H-plane behind GL as well as the F plane above GL; the part below GL represents that portion of the H plane anterior to GL as well as the F plane below GL. Fig. 3b is the orthographic representation of fig. 3a. a^F has not been affected by rotation of the H plane, but a^H has been brought below the ground-line. Between them is the dotted line of recall. It is perpendicular to GL, and intersects it at P. Point A is in the first quadrant (I). To visualize this from its projections, picture the paper as the H plane only, and GL as the upper edge of the F plane. Ignore a^F . a^H then shows that point A is anterior to the frontal plane by the distance, Pa^H . Then take the paper as the F plane, and GL as the anterior edge of the H plane. Ignoring a^H , we see that point A lies the distance Pa^F above the horizontal plane. A is therefore above and in front of GL. If O be taken as the null-point, A lies to its right by OP and above and in front of it by Pa^F and Pa^H , respectively. These are its XYZ, or Cartesian, coordinates.

In fig. 3c, line AB is represented orthographically by joining the respective H and F projections of points A and B. a^Fb^F and a^Hb^H are the frontal and horizontal projections of the line. It is in I, as shown pictorially in fig. 3d.

In fig. 4a, four points, A, B, C, and D are depicted, one in each of the dihedral angles. A is in I, B in II, C in III, and D in IV. By comparing with the orthographic representation of these points in fig. 4b, it is seen that:

A point in I has its H projection below and its F projection above GL.

A point in II has both projections above GL.

A point in III has its H projection above and its F projection below GL.

A point in IV has both projections below GL.

By well retaining the orientation of these four points, a faculty for visualization

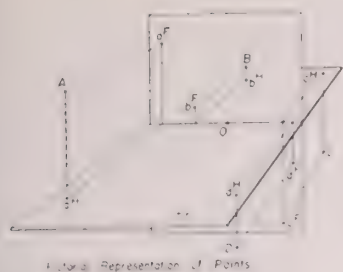


Fig. 4a



Fig. 4b

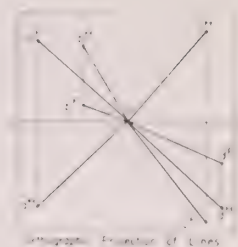


Fig. 4c

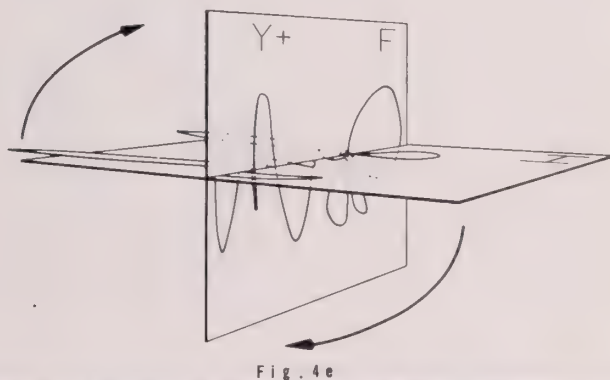
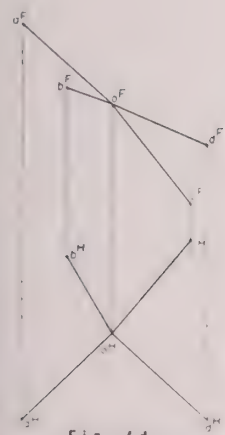


FIG. 4a. Pictorial representation of four points, one in each of the spatial quadrants. FIG. 4b. Orthographic representation of these points. A is in I, B in II, C in III, D in IV. FIG. 4c. By joining a^F and a^H to the null-point, 0, we construct the projections of vector OA. OB, OC, and OD are similarly formed. FIG. 4d. When the horizontal projections are moved *en masse* to a position below the frontal, the former comprise the "plan" of the spatial arrangement, the latter, the "elevation." FIG. 4e. The frontal projection of our case of left bundle-branch block and its vertical component, Y, are shown on the frontal plane. The horizontal projection and its sagittal component, Z, are on the horizontal plane.

of points and lines in their true spatial relationships can be acquired by most persons. Point 0 on the ground-line has, of course, both its projections on GL. By joining 0 to a^H , the horizontal projection of line OA is formed, as in fig. 4c. Oa^F is the frontal projection. Lines OB, OC, and OD, which may be taken as vectors originating at the null-point, are similarly represented by their projections. In practice, the horizontal projections are usually moved to a position above or below the frontal, as in fig. 4d, the former being the "plan" of the spatial arrangement, the latter, the "elevation." For analytic construction they are usually left superimposed.

In fig. 4e, the frontal projection of our case of left bundle-branch block and its vertical component, Y, are shown on the frontal plane, and the horizontal projection and its sagittal component, Z, on the horizontal plane. After rotation of the latter and separation of the projections, the loops are orthographically

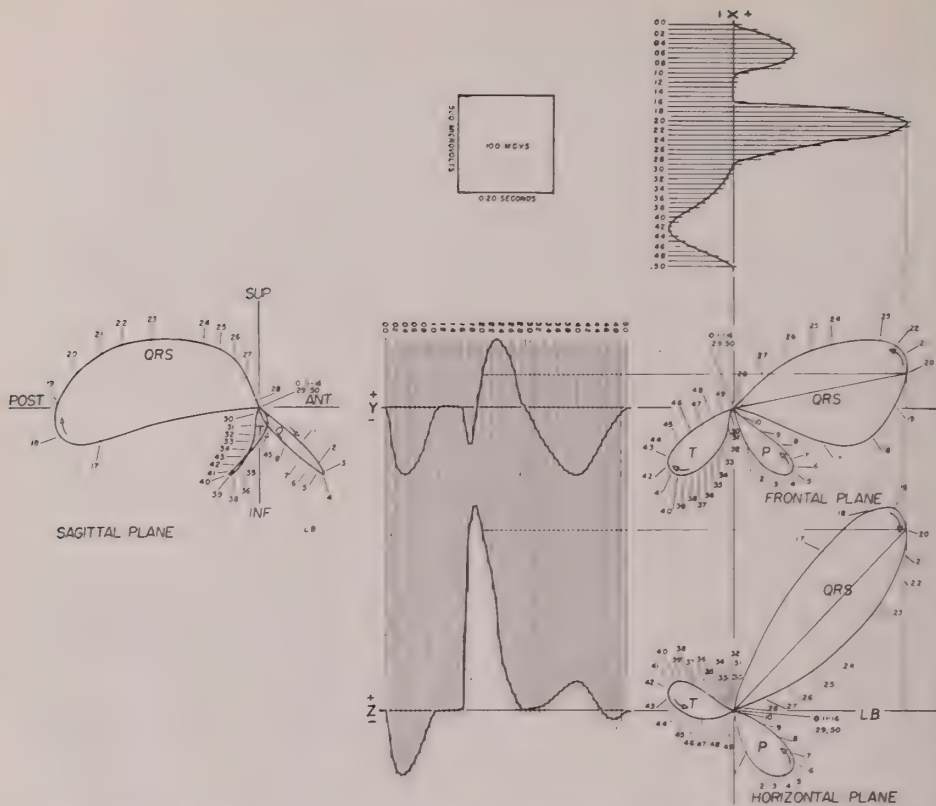


FIG. 5. Orthographic representation of the spatial loops. The derivation of the frontal and horizontal projections of one instantaneous vector, that at 0.20 seconds, is illustrated.

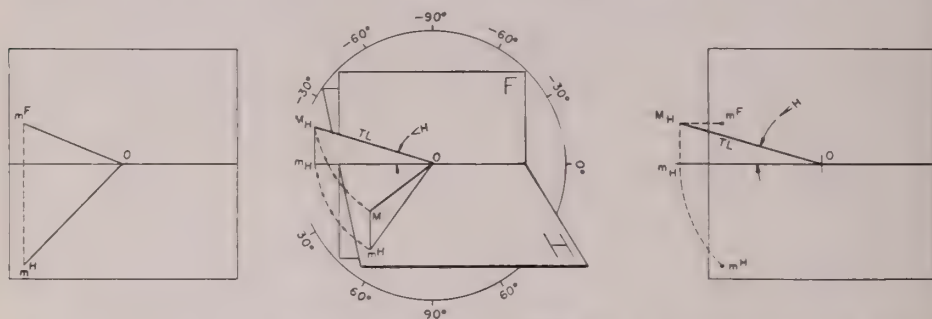


FIG. 6a. Orthographic representation of vector \overline{OM} . FIG. 6b. Determination of its true length (TL) and of the angle it subtends with the horizontal plane ($\angle H$) (pictorial representation). A plane is passed between the vector and its horizontal projection. This is its horizontal projecting plane and is perpendicular to the horizontal plane. When it is revolved into the frontal plane, TL and $\angle H$ present, as they have not altered during the revolution. They are the polar coordinates of point M on the horizontal projecting plane. M_H , the new position of M, is termed its horizontal revolute. $\angle H$, which is the elevation of \overline{OM} , is measured against the dial inscribed on the frontal plane. It ranges from 0° to $\pm 90^\circ$. Inferiorly directed angles are positive; superiorly, negative. FIG. 6c. Orthographic representation of the revolution. An arc centered at O is drawn from m^H to the ground-line. M_H is obtained by erecting a perpendicular at the point of intersection to the altitude of m^F .

presented, as in fig. 5. The horizontal projection is directed posteriorly and to the left, shows clockwise rotation, and slowing of the middle and late portions of its inscription (8). The sagittal projection is not necessary for visualization but finds application in the solution of certain types of spatial problems. In practice the projections are instantaneously obtained by leading the components to their respective terminals on the oscilloscope.

METHOD

Let us assume the vector, \overline{OM} , with projections, Om^H and Om^I , as in fig. 6a. The problem is to determine its true length (magnitude) and the angle it subtends with the horizontal plane. If we pass a plane between the vector and its horizontal projection, this plane will be perpendicular to the horizontal plane and is called a horizontal projecting plane. This has been performed in fig. 6 b. The plane, OMm^H , can then be revolved about O , remaining perpendicular to H , until it is superimposed on the frontal plane. The new positions of m^H and M are now m_H and M_H (subscripts denote positions after revolution). OM_H is the true length (TL) or magnitude, of the vector, and $\angle M_HOm_H$ is the angle sub-

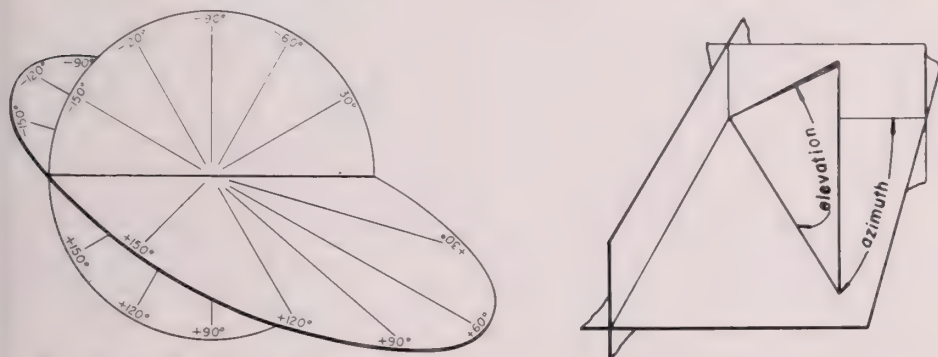


FIG. 7a. The Einthoven dial, when inscribed on the horizontal plane, serves for azimuth. This ranges from 0° to $\pm 180^\circ$. Anteriorly directed angles are positive; posteriorly, negative. FIG. 7b. Angular coordinates of spherical coordinate system. Azimuth is the dihedral angle between the horizontal projecting plane and the left half of the frontal plane and therefore equals the angle between the horizontal projection and the left half of the ground line. Elevation is the angular distance of the vector from the horizontal plane. Azimuth establishes the plane of the vector, and elevation and magnitude are its polar coordinates on that plane.

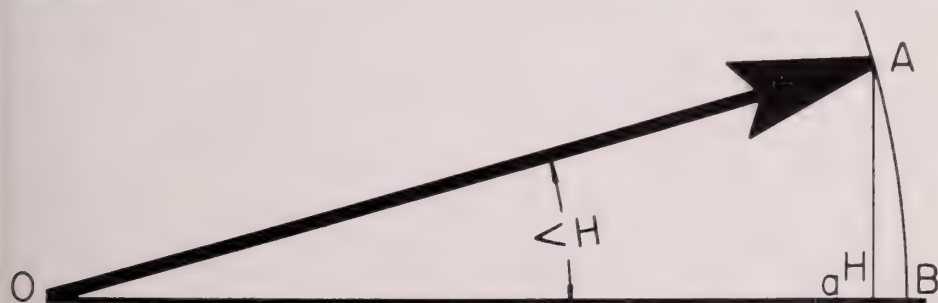


FIG. 8

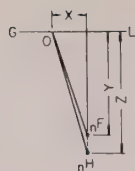


Fig. 9a

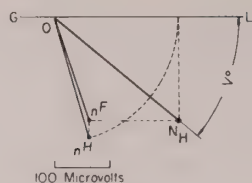


Fig. 9b

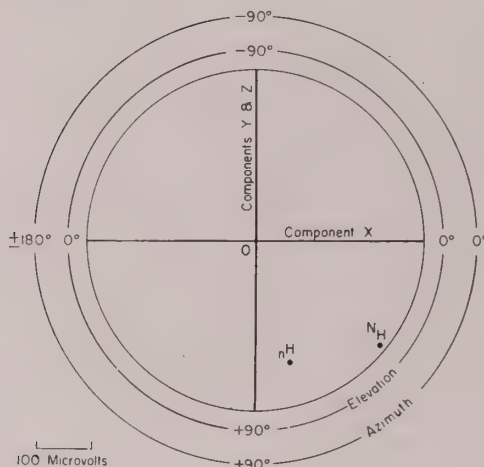


Fig. 9c

FIG. 9a. The instantaneous vector at 0.01 seconds is annotated as N . Its frontal and horizontal projections, n^F and n^H , are shown. Fig. 9b. Elevation and magnitude are determined by revolution. Fig. 9c. The revolution may be performed on a chart. The abscissa represents the ground-line; the ordinate, the edge of the sagittal plane. n^H is positioned from its components, N_H is determined, and the spherical coordinates read on the dials. M° , H° , and V° are 297 microvolts, 72.5°, and 39°, respectively.

tended with H by \overline{OM} , these having been unaffected by the revolution. The manoeuvre can be performed orthographically (fig. 6c). An arc of radius Om^H is drawn to the ground-line and a perpendicular, $m_H M_H$, erected to the altitude of m^F . OM_H is then the true length of \overline{OM} , and $\angle M_H Om_H$ is the angle \overline{OM} subtends with H *spatially*, or its angular distance from H ($< H$). As M_H has been determined by revolution of a horizontal projecting plane and furnishes angular distance from the horizontal plane, it has been termed the *horizontal revolute*.¹ Any vector, regardless of orientation, can be determined by this manoeuvre. Any system of electrode placement from which two projections can be derived is suitable (1, 21-26).

Vector \overline{OM} may now be set within a spatial reference frame, the *spherical*

¹ In a strict mathematical sense, a revolute is a solid of revolution, i.e., a space traversed by a surface during its revolution. In fig. 6b, this is the segment of a cylinder between the planes OMm^H and $OM_H m_H$. For simplicity in discussion, however, and as we are primarily interested in the final position of the terminus after revolution, M_H , this is here referred to as a revolute.

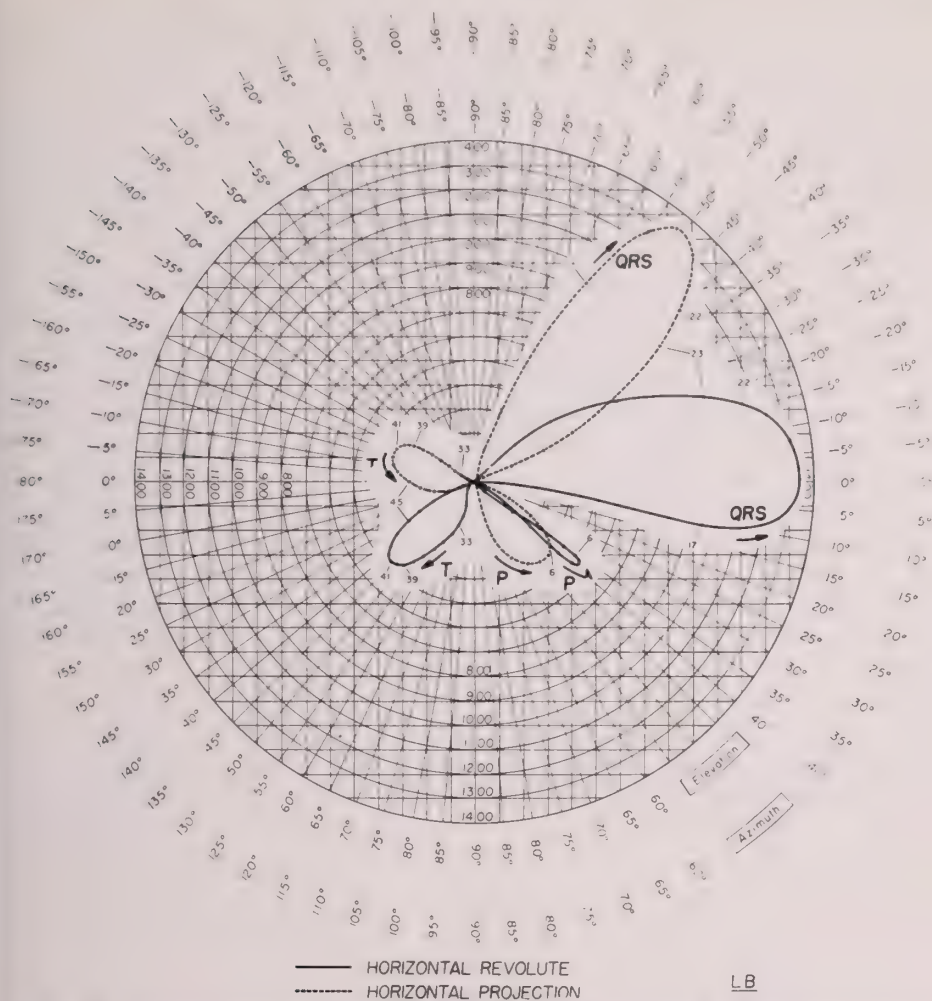


FIG. 10. The orthovectorcardiogram. If the horizontal revolutes of all the instantaneous vectors be determined and consecutively joined, a pattern is formed which may be termed the horizontal revolute of the cycle. It furnishes instantaneous magnitude and elevation. The latter is measured against the inner dial, the former against the concentric circles. The horizontal projection supplies azimuth (measured against outer dial). This representation of instantaneous spherical coordinates is termed the orthovectorcardiogram.

coordinate system (27). If we re-examine fig. 6b, we note that $\angle H$ and OM are the polar coordinates of vector OM on its horizontal projecting plane. In this system they are termed *elevation* and *magnitude* and annotated by the symbols, V° and M° , respectively. Elevation angles range from 0° to $\pm 90^\circ$. Those directed below the horizontal plane are positive; those above, negative.

The position of the horizontal projecting plane is denoted by its azimuth (H°). This is the dihedral angle it subtends with a prechosen plane, here the left half of the frontal. It equals the angle between the horizontal projection and the left half of the ground-line and ranges from 0° to $\pm 180^\circ$. Azimuth angles an-

terior to the frontal plane are considered positive; those posterior, negative, as in fig. 7a. Azimuth and elevation are illustrated in fig. 7b.

The principle of revolution and the spherical coordinate system may be illustrated in another manner. There is an arrow at the bottom of page 83 (fig. 8). If the journal be held open perpendicularly on a table, it may be taken as a frontal plane, and the table as the horizontal. If the page be held out, it becomes a horizontal projecting plane, on which are inscribed both the arrow, OA , and its horizontal projection, Oa^H . The position of the page relative to the (anatomical) left half of the journal is the azimuth. The magnitude and elevation of the arrow are the polar coordinates of its terminus, A , on the plane of the page. If the latter be slowly turned, there is an apparent decrease in magnitude and increase in elevation as it approaches the line of sight. This is equivalent to the alteration of these values as projected to the frontal plane. When the page is revolved into the journal, the coordinates present in their true values.

Let us determine the spherical coordinates of the first instantaneous vector of our case of left bundle-branch block, that at 0.01 seconds. Designated N , its components and projections are shown in fig. 9a, and construction for magnitude and elevation in fig. 9b. The revolution may conveniently be performed on the modified polar coordinate of fig. 9c. The projections are positioned, the revolution performed, and magnitude, azimuth and elevation read on the chart. M^0 , H^0 , and V^0 , are 297 microvolts, 72.5° , and 39° respectively.

The Orthovectorcardiogram

If the horizontal revolutes of all the instantaneous vectors be determined and successively joined, a pattern for the entire cardiac cycle is produced, which may

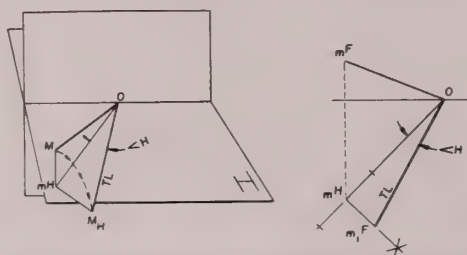


FIG. 11. Determination of magnitude and elevation by rotation of horizontal projecting plane into horizontal plane. $m^H m^V$ equals altitude of m^F .

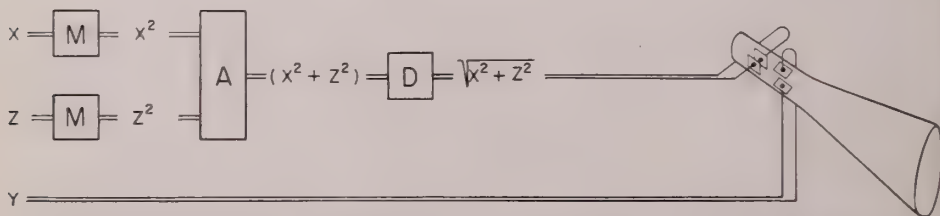


FIG. 12. Block diagram for instantaneous recording of horizontal revolute. M is multiplier; A , adder; D , for derivation of square root. Y is led to vertical plates of cathode-ray oscilloscope; $\sqrt{X^2 + Z^2}$, to the horizontal plates.

be called its *horizontal revolute*. This is shown as the solid line of fig. 10. In combination with the horizontal projection (interrupted line) it furnishes the instantaneous spherical coordinates throughout the cycle. The pair shall be termed the *orthovectorcardiogram*. Note that the revolutions can be performed visually with the aid of the graticulation on the chart. No instruments are required. Oscilloscopically recorded projections are manipulated in the same manner.

Elevation and magnitude have been determined by revolution of a horizontal projecting plane into the frontal plane. They can also be obtained by revolving the horizontal projecting plane into the sagittal plane or by folding it over into the horizontal plane. The pictorial and orthographic representation of the latter are shown in fig. 11. It amounts simply to the drawing of a hypotenuse to a triangle whose base is Om^H and whose altitude is the distance of m^F from the ground-line, or component Y . The disadvantage of this procedure is that elevation is measured on the horizontal plane from a varying axis, the horizontal projection, rather than on the frontal plane from a fixed axis, the ground-line.

The orthovectorcardiogram can be recorded electronically. It is readily calculated from fig. 6 that the Cartesian coordinates of the horizontal revolute, M_H , are Y and $\sqrt{X^2 + Z^2}$. If Y be led to the vertical plates of an oscilloscope, and $\sqrt{X^2 + Z^2}$ to the horizontal, the horizontal revolute will appear on the screen. Fig. 12 presents a block diagram of such a circuit.

SUMMARY

1. A simple method of determining magnitude and orientation in space of instantaneous vectors without calculation is described.
2. A new method of charting the electrical events of the cardiac cycle, the orthovectorcardiogram, is presented.
3. The basic principles of orthographic projection are reviewed.

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SERIAL OBSERVATIONS ON THE PHYSIOLOGICAL AND PSYCHOLOGICAL CHANGES IN PATIENTS REACTING WITH A DEPRESSION TO RESERPINE

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Recently there have been appearing in the literature an increasing number of reports of adverse reactions in patients following the administration of the Rauwolfia preparations; namely depression, depersonalization, psychoses, recurrence of peptic ulcer with bleeding, severe mucous colitis with ulcerations, exacerbations of pre-existing asthma, renal and biliary colic and death following the administration of electroshock therapy (1-6). These distressing and catastrophic reactions constitute a major contraindication to the indiscriminate use of these compounds. Since these drugs are very useful in treating many diseases, it obviously would prove worthwhile if some means could be found to detect those patients potentially vulnerable to the more serious side effects. This paper is a preliminary report of experimental work now in progress at The Mount Sinai Hospital, which it is hoped will shed some new light on this problem.

The following is a brief summary of previous experimental findings of the possible site and mode of action of Serpasil (7-8). The miotic action of Serpasil has provided the most profitable field of study. This effect is not very great in man, but in the dog and other animals it is the sign which appears first and persists the longest. If the eye is denervated by excision of the ciliary ganglion Serpasil has no effect, demonstrating that the drug does not act at the periphery. The miosis might then be due to central stimulation of the parasympathetic system or to central inhibition of the sympathetic system. The nictitating membrane of the dog and cat has no parasympathetic innervation; contraction of, and relaxation of this membrane are due to sympathetic stimulation and inhibition respectively. Serpasil causes relaxation of the nictitating membrane and this has been taken to support the view that Serpasil acts by central inhibition of sympathetic tone. Several other effects of Serpasil might be explained similarly; i.e. the increased intestinal motility and slowing of the heart. The clinical side effects of aggravated bronchial asthma, renal colic, biliary colic and ulcerative colitis might again be due to the inhibition of sympathetic tone and the relative parasympathetic dominance produced.

Patients who have been treated with Serpasil in the Department of Psychiatry at The Mount Sinai Hospital have been examined by the Funkenstein Test prior, during and subsequent to this form of therapy. The reasons for using this test on these patients was threefold; (a) from the experimental data cited it would appear that Serpasil effects the autonomic balance, (b) the Funkenstein

From the Department of Psychiatry, The Mount Sinai Hospital, New York City. Presented at the New York Society for Clinical Psychiatry, The Mount Sinai Hospital, April 12, 1956.

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Test is a sensitive indicator of this balance, (c) therefore by doing psychological and physiological serial studies on patients receiving Serpasil, we hoped to obtain a more comprehensive picture of whatever changes might occur. In particular we wanted to know whether Serpasil acts only on the patient's symptoms or whether it produces a more fundamental effect on the disease process.

The Funkenstein Test utilizes the intravenous administration of adrenaline (0.025 mg.) and the subcutaneous administration of mecholyl (10 mg.) to measure the autonomic balance of the patient. On the basis of the degree and duration of the hypertensive and hypotensive effects of adrenaline and mecholyl, Funkenstein (9-11) divided the patients into distinct groups (chart).

Group I: Epinephrine—rise in systolic blood pressure in excess of 50 mm. Hg. Mecholyl—slight fall in blood pressure (systolic) with early rise above pre-injection level and failure to return to the pre-injection level during the 25 minute observation period.

Group II and III: Epinephrine—rise in systolic blood pressure in excess of 50 mm. Hg. Mecholyl—moderate or slight fall in systolic blood pressure with or without slight rise above the pre-injection level but with establishment of homeostasis, i.e. return to pre-injection level of blood pressure and maintenance of it, within the 25 minute observation period.

Group IV: Epinephrine—rise in systolic blood pressure in excess of 50 mm. Hg. Mecholyl—moderate fall in systolic blood pressure with marked compensatory delayed rise before establishment of homeostasis (return to pre-injection level and maintenance of it for three to five minutes within the 25 minute observation period.)

Group V: Epinephrine—rise in systolic blood pressure of 50 mm. Hg or less. Mecholyl—fall in systolic blood pressure with failure to return to the pre-injection blood pressure level within the 25 minute observation period.

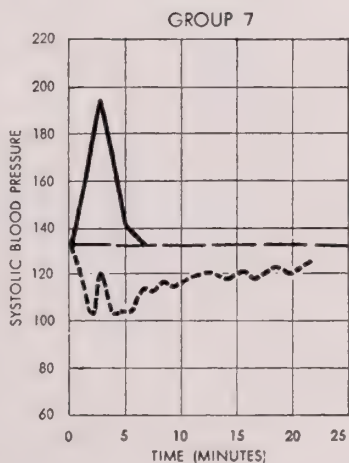
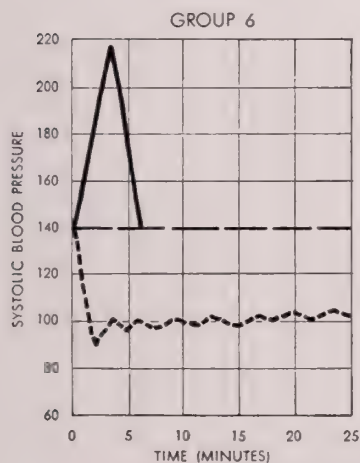
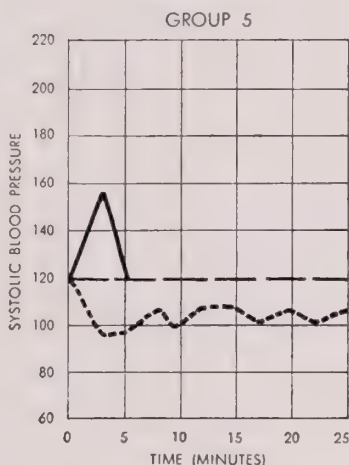
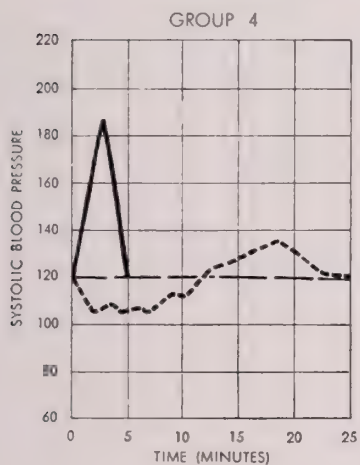
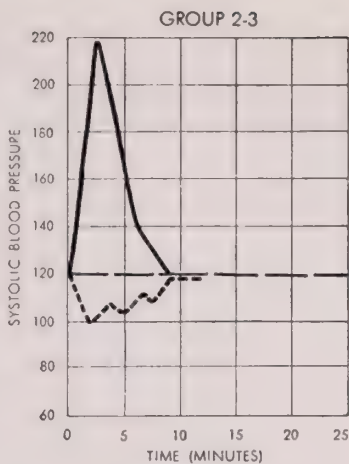
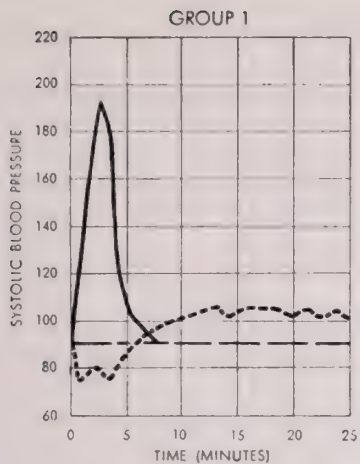
Group VI: Epinephrine—rise in systolic blood pressure in excess of 50 mm. Hg. Mecholyl—fall in systolic blood pressure with failure to reach pre-injection level of blood pressure within the 25 minute observation period.

Group VII: Epinephrine—In this group are included all cases in which a chill occurred after mecholyl. A reliable blood pressure curve could not be obtained because of noise engendered by the muscular contractures during the chill.

Group I and IV are therefore characterized by a hyper-reactivity of sympathetic-adrenal discharges in response to mecholyl; Group V, VI and VII show a hyporeactivity of this system, and Group II and III a normal sympathetic reaction (11).

Funkenstein made the fundamental clinical observation that the favorable response to electroshock therapy is linked with certain autonomic groupings; namely Groups VI and VII where there is a prolonged hypotensive response to mecholyl indicating a hypo-reactivity of the sympathetic centers. He found that this autonomic pattern was more reliable as a prognostic indicator for electroshock response than the diagnostic classification based on clinical symptoms. He also found that in successful electroshock therapy the altered mental state was associated with a change in reaction to mecholyl, i.e. from Group VI or VII

MECHOLYL-EPINEPHRINE TEST



Mecholyl Response - - - - -
 Epinephrine " - - - - -

to Group II or III. He concluded therefore that "... when the psychological picture changes the physiological picture changes and *v.v.*" That is, improvement of the clinical condition of the patient is associated with an alteration in the blood pressure reactions that are induced by mecholyl and adrenaline. If these reactions do not change, then the clinical picture is unaltered.

An obvious factor which merits consideration in research on psychophysiological responsiveness is the level of physiological activity which is being tapped by the particular measures employed. It is beyond the scope of this paper to present all the experimental data that validate the relationship between the injection of peripherally acting drugs such as mecholyl and adrenaline and the resultant blood pressure effects mediated by the central nervous system hypothalamic structures. Numerous experimental studies, Gellhorn (12) in particular, utilizing hypophysectomized animals, autonomic blocking agents and denervated peripheral preparations have shown that the degree and duration of the hypotensive effect of mecholyl are inversely related to the degree of sympathetico-adrenal discharges; that parasympathetic discharges play no role; and that it is the central nervous system structures that determine the resultant blood pressure effects.

MATERIALS AND METHOD

Fifty three unselected and consecutive patients admitted to the Department of Psychiatry of The Mount Sinai Hospital form the basis for this study (with the exception of six patients with either severe asthma or extensive cardiovascular involvement). These patients, in addition to the usual psychiatric workup, were examined by the Funkenstein Test prior, during and subsequent to various therapies (which in our series included hospitalization and observation only, superficial and intensive psychotherapy, electroshock and tranquilizing drug therapy). A report on the general findings of the fifty-three patients who have been studied in this manner, has been published (13). This paper is a preliminary clinical report, and is limited to those patients who demonstrated depression, depersonalization or untoward reactions to electroshock therapy following the administration of Serpasil.

Each patient under basal conditions, not having eaten for at least two hours, remained in bed for at least 30 minutes prior to testing. Systolic blood pressure was determined every three minutes. After a basal systolic blood pressure reading was obtained, the patient received 1 cc. of isotonic saline intravenously. The systolic blood pressure was then determined every minute for 10 minutes. On the next day, the patient received 0.025 mg. of epinephrine intravenously and the systolic blood pressure was followed at intervals of one minute until it returned to the basal level. On the third day, under similar basal conditions, the patient received 10 mg. of mecholyl subcutaneously, and the systolic blood pressure was followed for 25 minutes. During the administration of each drug, it was also noted whether the patient showed pallor, anxiety, flushing, sweating or a shaking chill. The results were demonstrated by superimposing the systolic blood pressure responses to mecholyl and adrenaline on the same graph (although the readings were obtained on different days).

RESULTS

The first group of patients demonstrate the so-called alternation of psychosomatic illness and depression or psychosis. Although the term "depressive equivalent" has been in vogue, they are equivalent only in the sense that they represent two different aspects of the broad way in which people handle their emotional activities. The following is an illustrative case; A 32 year old white married female was admitted with an acute exacerbation of chronic ulcerative colitis, which was of four years duration. Her physical symptomatology consisted of bloody stools, diarrhea, anorexia and a 15 pound weight loss. In addition, she presented the picture of marked psychomotor agitation and pan-anxiety. Her psychiatric diagnosis was obsessive-compulsive reaction with the possibility of an underlying psychosis. On admission her autonomic responsivity placed her in Group I or marked adrenergic hyperactivity.* In addition to other medical treatment, Serpasil 2 mg. was administered orally each day for the increased psychomotor agitation. Three weeks later the patient presented the clinical picture of a severe depression, and concomitantly had lost all of her somatic symptomatology referable to the ulcerative colitis. Autonomic testing at this time revealed that she had shifted from Group I to Group VI. Serpasil was withdrawn from therapy. Two weeks later the depression began to lift along with the return of her initial ulcerative colitic symptoms. Testing at this time revealed a Group IV response or moderate adrenergic hyperactivity. One week later all overt signs of the depression had disappeared. In addition to the complete return of her colitic symptoms, autonomic testing revealed that she had returned to Group I.

Another type of reaction to Serpasil was shown by a 49 year old white male admitted with a clinical picture of an atypical involuntional melancholia. He presented numerous somatic complaints referable to the respiratory system, marked agitation and a covert depression. On admission autonomic testing revealed a Group V reaction (a grouping indicative of a poor prognosis for electroshock). Three mg. of Serpasil was administered intramuscularly daily for the marked agitation, restlessness and insomnia. One week later the patient presented the clinical picture of a severe depression, with no somatic complaints. Testing at this time showed a Group VII reaction or marked cholinergic hyperreactivity with chills in response to mecholyl. Although Serpasil was discontinued, the depression persisted and appeared to become progressively worse. Twelve days after discontinuation of the Serpasil, autonomic testing disclosed a Group VI response; a grouping indicative of a good prognosis for electroshock therapy. Eight electroshock treatments were given and the patient's depression lifted dramatically. Retesting at this time disclosed a Group II reaction, or normal sympathetic reactivity. A six month follow-up revealed that the patient had maintained his clinical improvement, was back at work and had no somatic complaints. Along these lines, we have had one other case in which Serpasil appeared to act as a *primer for electroshock*, occurring in a patient who had not pre-

* Recent experimental evidence would tend to shift the emphasis to noradrenalin hyperactivity.

vously responded to electroshock therapy. After 2 mgm. of Serpasil was given orally each day for two weeks, he shifted to a favorable autonomic group, and responded well to six electroshock treatments.

Our series now includes a total of six cases that responded to Serpasil with a clinical depression or psychosis, and shifted to a predominantly parasympathetic response. In addition, these patients exhibited odd and chilly sensations, sensitivity to cold, dizziness, urinary urgency, a laxative effect and/or nasal stuffiness; all cholinergic manifestations. In general therefore, Serpasil-induced depressions in our series developed gradually and appeared primarily in patients for whom the drug had produced excessive cholinergic symptoms. This cholinergic hyperactivity being expressed symptomatically and by means of autonomic testing.

From the group of Serpasil-induced depressions requiring electroshock therapy, two patients demonstrated a diminished convulsive threshold to electroshock therapy. Experimental studies (9) indicate that electroshock excites the centers of the autonomic system and cause a sympathetico-adrenal and a parasympathetic (vago-insulin) discharge with the former predominating in normal organisms. The changes in the blood pressure following electroshock support this interpretation. The *initial fall* in blood pressure is however, vagal in origin. The evidence of these cholinergic effects are seen during all seizures induced with electroshock. The passage of electricity through the brain gives rise to such manifestations, even in the absence of overt seizures; i.e. flushing, hypotension, lacrimation and bradycardia. During overt seizures, there are in addition salivation and cardiac arrhythmias. These vagal effects are apparently prevented from becoming dangerous by the subsequent adrenergic discharge manifested by the late pallor, piloerection, hypertension and tachycardia which occurs during all convulsions.* Conceivably then, anything that disturbs the autonomic balance prior to electroshock therapy might cause untoward reactions by exaggerating the initial vagal effects of electrically-induced convulsions.

A possible explanation of the deaths, imperceptible vital signs for several minutes and the severe falls in blood pressure following electroshock, in patients who have received Serpasil, is indicated by the following considerations:

(a) In patients developing a Serpasil-induced depression, there is concomitantly produced a severe parasympathetic predominance (as shown by the Funkenstein Test).

(b) A further depression of the sympathetic side of the autonomic balance occurs with the administration of intravenous barbiturates prior to electroshock therapy (when a barbiturate is administered as an anesthetic, there is a marked drop of blood-adrenaline concentration).

(c) Electroshock therapy with its initial vagal response, potentiates the existing cholinergic hyperactivity produced by Serpasil and the barbiturates.

* One of the most plausible theories for the efficacy of electroshock, is the production of increased sympathetico-adrenal reactivity long after the shock treatments; this theory would be supported by changes in autonomic reactivity shown by the Funkenstein Test and would also account for the clinical observation that electroshock therapy without the convulsion (adrenergic stimulation) is therapeutically valueless.

It can be hypothesized therefore, that in the catastrophic reactions following electroshock in patients who have been on Serpasil, we are seeing a severe form of the vaso-vagal syndrome. From the autonomic tests that we have performed on patients receiving Serpasil, it appears to take almost two weeks for the excessive cholinergic reactivity to disappear. It would therefore seem that certain prophylactic measures are necessary before giving electroshock therapy to patients who have been on Serpasil. If at all possible, electroshock therapy should be postponed for at least two weeks after cessation of Serpasil. A test for carotid sinus hypersensitivity should be done before treatment is instituted. If there is evidence of excessive vagal activity, shock treatment should either be postponed or atropine should be administered before the electroshock is given.

SUMMARY

The following hypotheses emerge from this study:

1. Our observations on patients treated with Serpasil appear to be in direct accord with the conclusions reached by the experimental pharmacologists in their work with animals; namely, that Serpasil appears to act by central inhibition of sympathetic tone. The resultant cholinergic hyperactivity being manifested in our patients by overt autonomic parasympathetic symptomatology; in addition the cholinergic hyperactivity being manifested objectively by the Funkenstein Test.

2. The alternation of symptoms, namely somatic manifestations and psychological manifestations of psychosomatic illness, appears to be an autonomic as well as phenomenologic event; providing again another demonstration of the psychophysiological unity of the organism. In our study even the finest nuances of psychological events were found to have a corresponding differentiation at the physiological level.

3. The hypothesis of the production of a vaso-vagal syndrome was presented to explain the catastrophic reactions of patients receiving Serpasil, to whom electroshock is administered. Specific measures for prophylaxis were suggested.

The clinical application of our data would appear to be the following:

1. A careful analysis of the personality and physiological status of the following patients before Serpasil is administered; patients with peptic ulcer, asthma, mucous and ulcerative colitis, renal and biliary colic; excessive cholinergic activity might prove very detrimental in these cases.

2. Where parasympathetic side effects become conspicuous in patients receiving Serpasil, one should become alerted for the possible onset of a depression or psychosis.

3. It would appear from this study, that electroshock treatment should never be given to a patient receiving Serpasil; two weeks appears to be the minimum period of time after cessation of Serpasil therapy, for the employment of electroshock treatment.

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DISRUPTION OF THE POST-CESAREAN SCAR

REPORT OF 16 CASES

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In the three-year period ending December 31, 1955 there were 11,852 deliveries in the Department of Obstetrics of The Mount Sinai Hospital. Seven hundred and seven pregnancies (6.05%) were terminated by the abdominal route; 320 (2.7%) of these were secondary sections, and 387 (3.29%) were primary. Sixteen uterine scar ruptures were found at the 320 secondary sections, and incidence of five per cent or one rupture in every 20 repeat sections. It is hoped that a presentation of these findings together with a brief review of the experience of others may be of some value.

Any break in the integrity of the scar of the previous section is interpreted as a rupture, whether it be one centimeter or the entire length of the scar. The fate of post myomectomy or other uterine scars is not included in this paper. No disruptions were discovered on immediate exploration of the uterine cavity in 27 women who were delivered vaginally after a previous section.

The fact that a ruptured uterine scar was found once in every 20 secondary sections is cause for much concern. The realization that the behavior of the cicatrix is unpredictable in subsequent pregnancies has increased our respect for this scar.

Wolfson and Lancet (1) reported three ruptures in 130 repeat sections, an incidence of 2.3 per cent or one in 43 repeat sections. All had sensitivity of the old scar. Each had a trial of labor and all had previous classical sections. All of the infants died. There was no maternal loss.

Beacham and Beacham (2) presented 23 cases of rupture of scars of cesarean sections. Seventeen of the 23 patients were in labor at the time of rupture (3 lower segment and 20 classical scars). There were 6 maternal and 15 infant deaths. One case had had a vaginal delivery after cesarean section, her scar ruptured during her third pregnancy, her second vaginal delivery. One patient had two lower segment and one classical cesarean section. The scar of the latter ruptured during the fourth pregnancy.

Bill et al (3) reported 13 instances of rupture of cesarean section scars. All followed the classical type of operation, five before and eight after the onset of labor. The labor in these patients lasted from one to 12 hours. There were two maternal deaths.

Kletzhandler (4) analyzed 812 secondary sections and found six (0.73 per cent) ruptures. He collected 402 such cases from the literature and found that 141 followed a classical section, 55 after the transverse fundal incision, 87 after the vertical lower segment and five after the transverse lower segment operation.

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In 104 cases no information could be obtained about the type of operation. About four-fifths of the mothers survived and about four-fifths of the infants died as a result of the ruptured scar.

Bak and Heyden (5) reported 15 cases of rupture of scars of cesarean sections. Six were asymptomatic and discovered at the time secondary section was performed (3 classical, 2 low flap and one in a hysterotomy scar). Nine cases ruptured during labor. The length of labor ranged from one to 24 hours, and the pregnancies were of 32 to 42 weeks gestation. In only two of the 15 cases was the uterus repaired. There was no maternal mortality, but six infants were lost.

Watt (6) reported five cases, all of which followed previous classical operations. All of the mothers lived but all of the infants died. Two were at term and in labor when rupture occurred. The other three presented earlier during pregnancy; one at eight months, one at six months and one as early as five months of gestation. The last patient had had four previous classical sections. The uterus of one patient was repaired and the other four had Porro sections.

Brierton (7) presented 7 cases of rupture of uterine scars in 246 patients with previous cesarean operations; an incidence of 2.8 per cent. He added the seven cases to 19 collected from four others. Nineteen were through scars of previous classical sections and seven through scars of previous lower segment sections. Two occurred before the 28th week, three between 32 and 36 weeks and 21 were in the last four weeks of gestation. Sixty-one per cent were in labor at the time of rupture. Pain and abdominal tenderness were present in 88 per cent and shock in 34 per cent. Labor stopped in 32 per cent at the time of rupture. In each instance when labor stopped, the infant was found free in the abdominal cavity. There were 15 hysterectomies and 11 uterine repairs, five with tubal ligations. The maternal mortality was 3.8 per cent and the infant mortality was 46 per cent. In seven cases of complete rupture the fetus, the placenta, or both were free in the abdominal cavity.

Lane and Reid (8) reported their findings in 697 ward patients with previous caesarian sections (451 lower segment and 246 classical) who had 583 secondary sections and 114 vaginal deliveries (89 after classical and 25 after low flap sections). There were 16 ruptures in 583 secondary sections, an incidence of 2.7 per cent and nine ruptures in 231 secondary sections performed on private patients or 3.9 per cent. Of the 16 ruptures in ward patients, 14 were in lower segment and two were in classical scars. In the 89 delivered vaginally, after the classical operation, one rupture occurred during labor. In the total of 25 ruptures 19 were in the vertical (Kroenig) lower segment scars, four in the transverse (Kerr) lower segment scars and two in the classical scars. There was no maternal mortality but three infants were lost.

Chesterman (9) reviewed the records of five hospitals and found 1,874 women who had become pregnant following a previous cesarean section. There were 33 cesarean scar ruptures, an incidence of 1.76 per cent. In 14 cases the scar ruptured before labor. Chesterman (9) mentions Holland, who in 1920, investigated the results of 448 pregnant women who had had a previous cesarean section. Four per cent of the scars ruptured, a figure that is much quoted. Chester-

man attributes his low incidence to better surgical techniques and the increased use of the lower segment operation. In another series of cases he analyzed the circumstances in which ruptures occurred. He found that 23 ruptures were through the previous classical scar (7 before and 16 during labor), and 15 (5 before and 10 during labor) followed the lower segment scar. Nearly all of the ruptures of scars of classical sections were complete and either the fetus, or the placenta, or both had escaped into the peritoneal cavity. In no instance did this happen after rupture of a lower segment scar, although in one case the rupture was complete. Rupture of the scar of classical sections was responsible for two maternal and 17 infant deaths. Rupture of 15 lower segment scars was responsible for no maternal and only one fetal death.

Cosgrove (10) presented 500 cases who had been delivered at the Margaret Hague Maternity Hospital following a previous cesarean section. Three hundred and twenty-one (64.2 per cent) had had a cesarean section repeated one or more times and 179 (35.8 per cent) were allowed to deliver vaginally one or more times. There were no maternal deaths incident to vaginal delivery after a cesarean section or due to the rupture of the scar of the previous section. There were five complete ruptures and all were through scars of previous classical sections, with extrusion of the fetus, or the placenta, or both through the scar. All the fetal deaths were in this group, and half of the infants were lost before the 38th week of gestation. There were seven incomplete ruptures of the uterine scar. Three occurred prior to labor and all were through the lower segment scars, either transverse or vertical. There were no maternal or infant deaths in this group.

In our 16 cases of rupture of cesarean section scars, the ages ranged from 22 to 37 years (Table I). In 15 patients the previous section was the lower segment type only and in one patient there were two previous classical and one lower segment operation. Five patients had two previous low flap sections. One patient had three previous sections (2 classical and one lower segment) and ten patients had only one previous section. There were seven ward and nine private patients. All were near or at term. In ten, the original section had been done for disproportion. One was performed because of toxemia, three for fetal distress, one for premature separation of the placenta and the indication for one was unknown. Of the 16 lower segment operations, there were two vertical and 14 transverse incisions. One patient had had two previous classical cesarean sections before she had a transverse low flap operation. The time interval between the present cesarean section and the last previous one was one to six years, in our series. Only one patient gave a history of previous post-section morbidity. Two patients had been previously operated upon at The Mount Sinai Hospital, both were of the transverse lower segment type, and the other 14 patients had their previous operations at other institutions.

Five patients (1 private and 4 ward) were allowed a trial of labor in the present pregnancy. The indication for the previous section was fetal distress in one and disproportion in four. Pelvimetry in the four latter cases showed adequate pelvis for vaginal delivery. Two of the five patients developed signs suggestive of rupture. One complained of sudden acute pain after ten hours of labor, and

TABLE I
Analysis of 16 cases—post section scar ruptures

Age	Para	Prim. Ward	No. Sect.	Indication First Section	Type Section Incision	Yrs. Rel. Last & Current Sect.	Prev. Morbid.	Labor Now	Scar Pain	Matern. Mort.	Fetal Loss	Size of Separation	Procedure	Trans- stions
1	23	1011	W	1	C.P.D.	L.F.-Trans.	4	0	Trial	None	0	2 cm.	Low flap—repaired	0
2	32	3033	P	3	Fetal distress	Class	3	0	None	Mild abd pain	0	Complete thru old class.	Subtotal hysterectomy (bleeding)	2
3	22	2022	P	2	C.P.D.	L.F.-Trans.	2	0	None	None	0	8 cm.	Low flap repaired, tubal ligation	0
4	33	2002	P	2	C.P.D.	L.F.-Vert.	1	0	None	None	0	8 cm.	Subtotal hysterectomy (bleeding)	0
5	24	2002	W	2	?	L.F.-Trans.	2	0	None	None	0	4 cm. elbow	Subtotal hysterectomy (sterilization)	2
6	28	1001	P	1	C.P.D.	L.F.-Trans.	4	0	None	None	0	4 cm.	Low flap—repaired	0
7	25	2001	P	2	C.P.D.	L.F.-Vert.	1	0	None	None	0	4 cm.	Low flap repaired, tubal ligation	0
8	34	1011	W	1	C.P.D.	L.F.-Vert.	1	0	Trial	Sudden acute	0	6 cm. elbow	Low flap repaired	3
9	34	1001	P	1	Fetal distress	L.F.-Trans.	2	0	Trial	Exquis. ten- derness	0	6 cm.	Subtotal hysterectomy (bleeding)	2
10	32	1001	W	1	C.P.D.	L.F.-Trans.	4	0	Mild	None	0	Complete	Low flap repaired	0
11	35	2002	P	2	Toxemia	L.F.-Trans.	4	0	Mild	None	0	5 cm.	Subtotal hysterectomy (bleeding)	5
12	32	1001	P	1	Fetal distress	L.F.-Trans.	6	0	0	None	0	8 cm.	Subtotal hysterectomy (bleeding placenta previa)	6
13	37	1001	P	1	Prem. sep. placenta	L.F.-Trans.	3	0	0	None	0	10 cm.	Low flap repaired	0
14	31	1001	W	1	C.P.D.	L.F.-Trans.	1	0	Trial	None	0	8 cm. shoulder	Low flap repaired	0
15	32	1001	W	1	C.P.D.	L.F.-Trans.	2	0	Trial	None	0	4 cm.	Low flap repaired	1
16	28	1011	W	1	C.P.D.	L.F.-Trans.	5	0	None	None	0	2 cm.	Low flap repaired	0

the other had no subjective pain, but exquisite tenderness on palpation of the lower segment after six hours of labor. The other three patients had the section performed because labor was not progressing satisfactorily, but at no time did they exhibit any subjective suprapubic pain or tenderness. Another patient who had been scheduled for an elective section was admitted at 36 weeks because of early labor. She had had two previous classical sections; her third section was of the transverse low flap type. Examination on admission showed no shock, no bleeding, but no fetal heart sounds were present. A ruptured uterus was suspected and at laparotomy the abdominal cavity had much free blood and the fetus with its sac intact, was found free in the peritoneal cavity. The uterus had contracted. The rupture was through the scar of a previous classical section. The infant was dead and a subtotal hysterectomy was performed.

Of the ten patients who were admitted for elective secondary sections, none had pain or tenderness of the old scar; three were in early labor.

The size of the disruptions ranged from two centimeters to complete separation of the scar. Half of the patients had simply the small separation beneath the bladder flap which extended under the eye as the operator developed his bladder flap. In these five cases, the bladder acted as a splint keeping the edges of the scars coapted. As soon as the splint was removed, the wound edge drew apart. In three cases, an extremity partially protruded through the site of rupture and as mentioned above, in another case, the fetus was free in the abdominal cavity.

Treatment of the uterus after it had been emptied depended upon the patient's age, her parity, the amount of bleeding, and the condition of the surrounding uterine tissue. The ruptured scar was trimmed and repaired in ten cases. Two of these had tubal ligations. There were six subtotal hysterectomies; one patient had three previous sections; three had two and two had one. All had previous lower segment operations and one had two previous classical sections before the low section. Four of the six hysterectomies were done because of extensive bleeding; one for sterilization and one because of complete rupture with the fetus in the abdominal cavity.

There was no maternal mortality and one infant was lost (6.6%) in the 16 cases of rupture of caesarean section scars.

The fact that all of the women and 15 of the 16 infants survived should not cause indifference, since rupture of caesarean section scars is always dangerous and may be fatal.

There is no accurate method of evaluating the competency of uterine scars, although the literature is full of various criteria for assessing its reliability and probable behavior in subsequent pregnancies. Pyrexia, due to infection of the uterine surgical wound may mean poor healing of the incision and therefore increased possibility of subsequent rupture. Yet only one patient in our series gave a history of previous infection. The absence of previous infection does not therefore preclude rupture. Faulty technique in closure of the uterus has been suggested as a cause of rupture of uterine scars resulting from caesarean sections. Either the incision has been closed too enthusiastically causing a strangulation

necrosis of the tissues or too few sutures caused incomplete approximation with resultant poor healing. Some authors stress the importance of careful angle closure to insure a firm scar. Careful approximation of the uterine musculature is purported to cause less scarring yet the fibrous tissue may be less likely to rupture than muscle. Even if the scar is exposed to inspection, it is claimed that no one can assess its true strength by its appearance. A thin scar may be extremely tough and strong. The thickness of a scar therefore is not a true index of its competency in labor or even in pregnancy. Still others feel that a scar presenting any irregularities or depressions is more likely to rupture. Some feel that the soundest scar results from an elective section before the onset of labor, contrary to the concept that the best scars are obtained during labor when the lower segment is well formed.

Because uterine scars do rupture, the type of incision to make in the lower segment is much debated. One finds as many enthusiasts for the longitudinal as for the vertical incision. Both incisions have their drawbacks. The transverse incision carries the danger of lateral extension into the sinuses and uterine arteries. The vertical incision, on the other hand, is rarely confined to the lower segment and almost always partly extends into the fundal portion. Its extension downwards may injure the bladder and even cause serious bleeding at its lower angle.

With the concept that defective healing may alter the shape of the uterus or the cervical canal, hystero-graphy has been advocated about three months after the initial section, in an attempt to detect a weak scar and evaluate its behavior in subsequent pregnancies. A lateral view may offer a valuable guide as to the mode of management of subsequent pregnancy and labor. We have had little experience with this preconceptional evaluation of the scarred uterus.

Many stress the importance of subjective pain and tenderness on palpation as a means of evaluating the condition of the uterine scar. The term "silent rupture" itself emphasizes the fallacy of depending upon signs and symptoms to detect separation. Hemorrhage and shock, so common in the classical picture of traumatic uterine rupture, are rarely present in cases where there has been rupture in the lower segment. Palpation of the uterine scar through the abdominal wall gives very little information since it is most applicable to the classical section scar. With the almost exclusive use of the lower segment operation, palpation of this scar above the symphysis becomes even more difficult. There are many who claim that it is easy to detect impending or actual rupture by subjective pain and scar tenderness, but how does one differentiate between the pain and tenderness accompanying strong normal labor? The converse is also true. We have submitted several patients to emergency laparotomy who, near term or in early labor, complained of tenderness or pain in the scar area, and found a totally intact uterus.

The concept that separation occurs more frequently in patients who have had classical operations is no longer true, since so few classical operations are now performed. However, it is our opinion that percentage-wise, rupture after a classical is more common than rupture after the lower segment operation.

Much has been written and will be written explaining why the uterine scar separates; how to detect its strength and weakness by palpation; how to evaluate its competency and its subsequent behavior by x-ray; how to eliminate the pitfalls in surgical technique and how to recognize separation in late pregnancy and during labor. Nevertheless an air of pessimism still prevails, for there is no answer at present, and there is no adequate means of evaluating the competency of the post section scar. It is important to keep in mind that every woman who has a scar in her uterus as a result of a section is a potential candidate for rupture in subsequent pregnancy.

To quote Beacham (2): "Even if one knows why, where, by whom, how and when the cesarean was performed, one still cannot vouch for the integrity of the scar, even though the postoperative course was smooth."

SUMMARY

1. Sixteen separations or disruptions of previous cesarean section scars have been found in 320 repeat sections done at The Mount Sinai Hospital from 1953 to 1955 inclusive. An incidence of five per cent, or one in every 20 secondary sections was found, which is very high in comparison to other reported series.

2. Fifteen of these cases were preceded by a low cervical operation. Only two of the patients had their previous cesarean section at The Mount Sinai Hospital.

3. There were no maternal deaths and only one fetal loss and that was through her only previous classical section scar, the two lower section scars being found intact.

4. One patient had subjective pain, one had exquisite tenderness but no pain, and another thought she was in early labor.

5. Ten uteri were repaired, two accompanied by tubal ligation and six uteri were removed.

6. The only case with a dead fetus followed a previous classical operation.

7. The time interval between present and last previous section was one to six years.

8. There were 13 separations of the previous transverse and two separations of the previous vertical scars in the 15 lower segment ruptures.

9. A patient who showed at elective repeat section a 4 cm. separation of a transverse lower segment scar and who had the scar repaired returned 29 months later for her third elective section. At that time the repaired scar was firmly healed with no defect.

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THE CORRELATION BETWEEN THE VECTORCARDIOGRAM AND POST-MORTEM FINDINGS IN RIGHT VENTRICULAR HYPERTROPHY

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INTRODUCTION

Certain congenital and acquired cardiac lesions produce ventricular hypertrophy, the recognition of which is a most valuable clue in differential diagnosis. Several reports dealing with the diagnosis of ventricular preponderance have been published from this laboratory (1-13). These studies were based on clinical examinations, laboratory investigations, cardiac catheterization, angiocardiographic data, and surgical confirmation. It is the purpose of this communication to correlate the postmortem findings in patients with unilateral right ventricular hypertrophy with their respective vectorcardiograms and electrocardiograms.

MATERIALS AND METHODS

The sixteen patients included in this report were studied at The Mount Sinai Hospital, New York. Their ages ranged from seven weeks to sixty-five years. Nine were females and seven were males. Eleven patients had cardiac catheterization performed. Vectorcardiograms were obtained using the cube system of electrode placement (14) with a Technicon or Sanborn oscilloscope. Electrocardiograms were recorded with a Technicon three channel direct writing cardiograph or a Sanborn Viso-Cardiette.

All sixteen patients died and had detailed gross and microscopic examination at necropsy. Observations, measurements, and descriptions were taken from the fresh specimen before fixation. In determining the presence of anatomic unilateral right ventricular hypertrophy, the criteria employed by us can be summarized as follows:

(a) The heart weight exceeded the mean standard deviation from normal for age, size, and sex. The normal and standard deviation was derived from Zeek's statistical analysis for individuals twenty-one years of age or older (15), and Coppoletta and Wollbach's analysis for individuals between birth and twelve years of age (16).

(b) The thickness of the right ventricular wall was 5 mm. or greater (15-22).

(c) The thickness of the left ventricular wall was less than 13 mm. (23). (Values greater than 13 mm would be indicative of left ventricular hypertrophy).

The vectorcardiographic and electrocardiographic criteria recently described

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TABLE I
Unilateral Right Ventricular Hypertrophy

Patient	Age	Sex	Diagnosis	Heart Weight (gm)	Normal Weight (gm)	Thickness (mm)		Diagnosis			Right Ventricular Systolic Pressure (mm Hg)
						RV	LV	ECG†	VCG‡		
									(Braunwald et al)	Type	
1) A. M.	5	F	Tetralogy of Fallot	150	85	8	8	RVH	RVH	II	
2) A. B.	35	F	Tetralogy of Fallot	270	231 ± 30	H*	N	RVH	RVH	I	99
3) J. C.	21	M	Tetralogy of Fallot			17	12	RVH	RVH	II	112
4) R. S.	8	M	Tetralogy of Fallot	230	110	10	N	RVH	RVH	III	150
5) Q. W.	53	F	Cor Pulmonale	370	222 ± 20	5	N	RVH	RVH	II	68
6) M. K.	26	F	Cor Pulmonale	280	254 ± 30	11	8		RVH	IV	79
7) M. B.	27	F	Cor Pulmonale	324	249 ± 30	7	N		RVH	II	67
8) M. R.	60	F	Cor Pulmonale	400	272 ± 30	H*	N	RVH	RVH	II	118
9) S. B.	65	M	Mitral Stenosis	500	296 ± 40	6	12	RVH	RVH	II	68
10) E. J.	41	F	Mitral Stenosis	380	258 ± 30	12	N	RVH	RVH	II	
11) J. M.	57	M	Mitral Stenosis	480	258 ± 40	H*	N	RVH	RVH	II	100
12) H. M.	30	M	Mitral Stenosis	600	340 ± 40	15	N	RVH	RVH	III	85
13) J. S.	6½ mos	F	Anomalous pulmonary venous drainage	192	31	13	4	RVH	RVH	II	
14) B. S.	24	F	Patent ductus arteriosus with reversal of the shunt	400	259 ± 30	30	N	RVH	RVH	II	113
15) D. S.	4 mos	M	Transposition of the great vessels	50	27	6	5	RVH	RVH	II	
16) G. G.	7 wks	M	Transposition of the great vessels	45	21	8	10	RVH	RVH	II	

* Hypertrophy.

† Electrocardiographic.

‡ Vectorcardiographic.

in this laboratory for determining the presence of unilateral ventricular hypertrophy were employed in the analysis of the records (6-13).

RESULTS

Table I shows the distribution of cases by age, sex, and diagnosis, and includes the heart weight, thickness of the right and left ventricles or a description of them, the electrocardiographic and vectocardiographic diagnosis, and the systolic right ventricular pressure levels.

It was found that all of the patients satisfied the anatomico-pathologic criteria described previously for unilateral right ventricular hypertrophy.

The vectocardiograms all disclosed right ventricular hypertrophy and were divided into four groups on the basis of the vectocardiographic configuration as previously reported in detail (7, 13). One patient had right ventricular hypertrophy Type I (Figure 1); twelve patients had Type II; two patients, Type III; and one patient, Type IV (Figure 2).

The QRS loop was mainly oriented anteriorly (H and S), more to the right than normal (H and F), and either superiorly or inferiorly (S and F). The direction of inscription of the QRS loop in the horizontal plane was clockwise in Types I and II; figure-of-eight in Type III; and counterclockwise in Type IV.

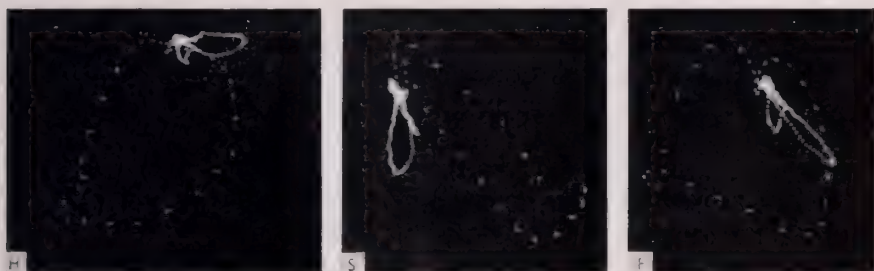


FIG. 1A. Spatial vectocardiogram of a 35 year-old female (#2) with tetralogy of Fallot. H = horizontal plane, S = sagittal plane, F = frontal plane. This vectocardiogram is typical of Type I (see text). Note the anterior orientation of the QRS loop and its clockwise inscription. Note the P loop directed anteriorly, inferiorly and to the left indicating right atrial enlargement.

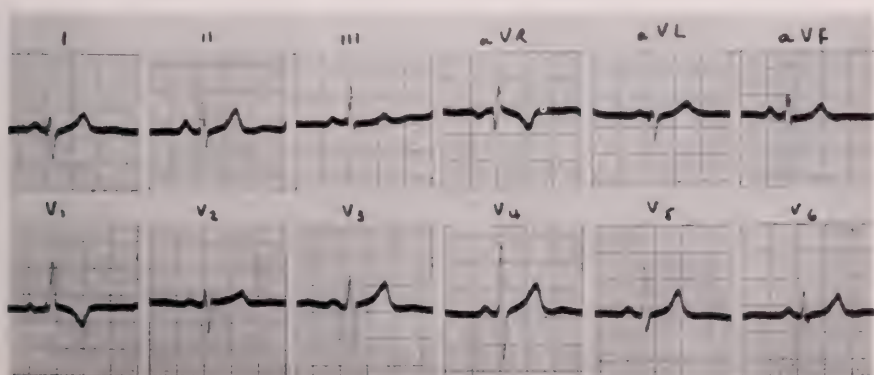


FIG. 1B. Electrocardiogram of patient whose vectocardiogram is shown in Figure 1A

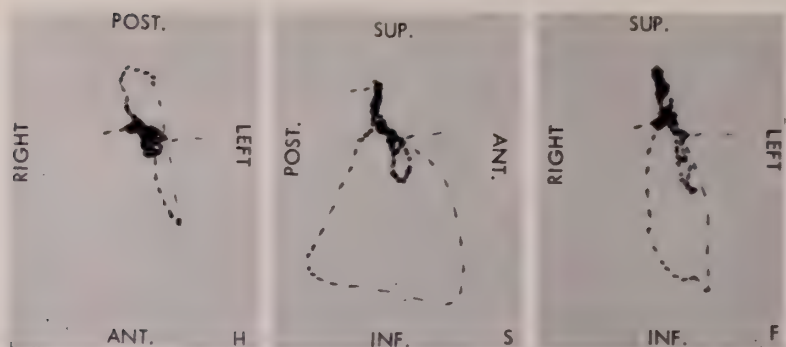


FIG. 2A. Spatial vectorcardiogram of a 26 year-old female (#6) with cor pulmonale. The QRS loop is characteristic of Type IV. It is oriented predominantly anteriorly to the isoelectric point, but it is inscribed in a counterclockwise direction in the horizontal plane. Note P loop oriented anteriorly, inferiorly and to the left.

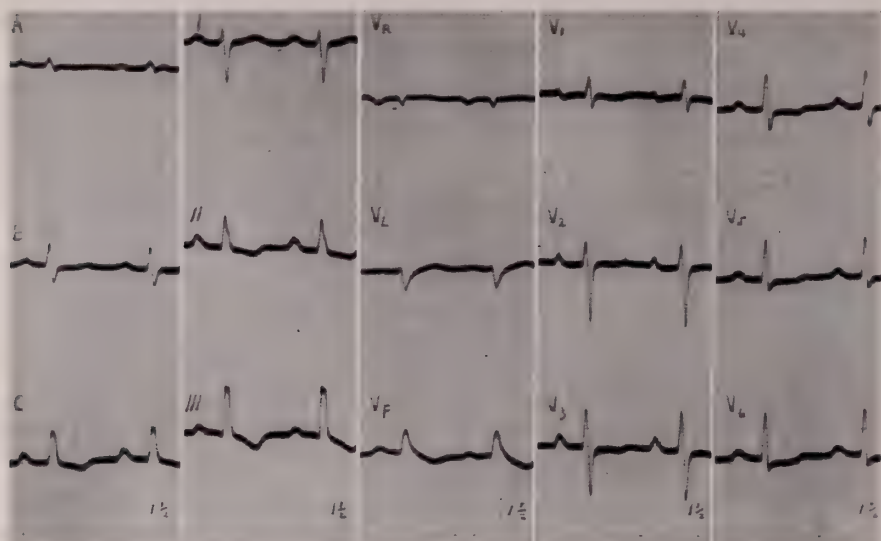


FIG. 2B. Electrocardiogram of patient whose vectorcardiogram is shown in Figure 2A

In the sagittal plane, nine had a counterclockwise inscribed loop, four a clockwise direction, and the remaining had a figure-of-eight loop.

The T loop orientation was discordant in ten, concordant in two, and revealed angular deviation in four.

The electrocardiograms revealed right ventricular hypertrophy in fourteen of the sixteen patients when the criteria proposed by Braunwald and associates (6) were applied.

The right ventricular systolic pressures obtained at the time of cardiac catheterization ranged from 67 to 118 mm Hg. The right ventricular thicknesses ranged from 5 to 17 mm.

DISCUSSION

The different types of heart disease represented in this series of patients characteristically produce hypertrophy of the right ventricle. The pathologic-anatomic findings concur with these observations. The vectorcardiograms obtained by the cube system indicated the presence of right ventricular hypertrophy in every instance. This correlation further emphasizes the accuracy and validity of the cube system of vectorcardiography in the diagnosis of right ventricular hypertrophy.

The electrocardiogram demonstrated the presence of right ventricular hypertrophy in fourteen of the sixteen patients when the criteria of Braunwald et al were employed. It should be reemphasized that the purpose of these criteria is to make it possible to establish the diagnosis of unilateral ventricular hypertrophy with confidence. These criteria are based on the maximum normal values for voltage and ventricular activation time compiled by Kossmann (24) and are not expected to detect all patients with ventricular hypertrophy. However, the observation that only two of the sixteen patients with anatomically proved right ventricular hypertrophy failed to satisfy these electrocardiographic criteria evidences their usefulness.

It has been suggested that an association exists between the level of right ventricular pressure and the vectorcardiographic type of right ventricular hypertrophy (4, 7, 13, 25, 26). Thus, the lowest pressures have been found to be associated with Type I vectorcardiograms and the highest with Type III vectorcardiograms. This type of association was not observed in our series since there was considerable overlap in the ventricular pressures when compared with the vectorcardiographic types (Table I).

The thickness of the right ventricle did not correlate in any manner with the type of vectorcardiographic pattern nor did the age of the patient.

This series of patients is a relatively small one, with a wide distribution of age and etiology of heart disease, and unequally distributed insofar as vectorcardiographic types are concerned. For these reasons, despite the lack of correlation observed, no definite conclusions concerning the relationships of myocardial thickness, age or pressure values with specific vectorcardiographic patterns can be made. Evaluation of larger numbers of patients which is continuing in this laboratory will clarify these matters.

SUMMARY AND CONCLUSIONS

1. Sixteen patients with proved anatomic unilateral right ventricular hypertrophy have been studied.
2. The vectorcardiogram demonstrated the presence of right ventricular hypertrophy in all instances, while the electrocardiogram was positive in fourteen of sixteen patients.
3. The vectorcardiogram as taken by the cube system is a valuable tool in the diagnosis of unilateral right ventricular hypertrophy.

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THEODORE BILLROTH AND THE BEGINNING OF GASTRIC SURGERY

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The Nineteenth Century was a century of vast social and intellectual progress. Its achievements included the Industrial Revolution, the emancipation of serfs and slaves, and advances in social legislation. The arts flourished, and fundamental discoveries were made in all branches of medicine and in many other branches of science. It saw the rise of such great medical men and ideas as Louis Pasteur and the Germ Theory, Joseph Lister's contributions to antisepsis, the introduction of anesthesia by Jackson, Morton and Souberean, the doctrine of cellular pathology promulgated by Rudolph Virchow and the advances in basic physiology made by William Beaumont and Claude Bernard. Surgery was elevated and broadened by James Marion Sims, Valentine Mott, Kocher, Treves, Mikulicz, Czerny and Astley Cooper. It was in this period of revolutionary change and colossal achievement that Theodore Billroth lived and that gastric surgery had its beginning.

In the Nineteenth Century the three great medical centers of the world were Paris, Berlin, and Vienna. Prominent medical scholars journeyed there, were trained in new techniques and concepts, and became leaders in other lands. In this way, the heritage of surgery at The Mount Sinai Hospital can be traced directly to the University of Vienna and to Dr. Theodore Billroth, for Dr. Arpad G. Gerster, was a student in Vienna in the 1860's.

Billroth was born in Prussia in 1829 at about the time that William Beaumont was studying gastric physiology on his celebrated patient, Alexis St. Martin. Billroth's life span was approximately parallel to that of Pasteur. In his early youth Billroth showed promise as a gifted pianist and intended to pursue music as a career. However, his mother, a martinet, persuaded the young man to undertake the study of medicine with a family friend, Professor Baum of the University of Gottingen. Although Billroth became a master in surgery, he never relinquished the study and enjoyment of music. Moreover, he believed that the study of music aided his inventive ability as a surgeon. He wrote: "It is one of the superficialities of our time to see in science and art two opposites . . . imagination is the mother of both" (2).

In 1851, Billroth went to the University of Berlin, where he came under the influence of Von Langenbeck and Von Graefe in surgery, and of Traube in experimental pathology; and here, under the tutelage of Von Langenbeck, one of the most celebrated operators of the Nineteenth Century, Billroth developed his brilliant surgical technique. In 1853 there were three months of unsuccessful private practice in which not one patient sought his surgical advice. This early setback failed to deter him, for he was destined to achieve fame by his studies

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FIG. 1. Christian Albert Theodor Billroth (1829-1894). From "Beiträge zur Chirurgie" (1).

on septic fever and wound infections, by his pioneer surgery on the esophagus and larynx, as the first surgeon successfully to perform a partial gastrectomy, and as the founder of a great school of surgery.

After several years as instructor in pathologic histology and anatomy and as an assistant to Von Langenbeck, Billroth in 1860 accepted the professorship of surgery at the University of Zurich. At Zurich he introduced the use of rectal temperature measurement in postoperative patients; moreover, he performed

extensive animal experiments on the effect of operation on body temperature (3). This research formed the basis of later investigations on wound infection and "Wundfieber." It should be remembered that Billroth was doing this advanced work at a time when bacteriology was just beginning, and surgery was giving birth to antiseptics. Louis Pasteur had recently shown that micro-organisms caused the fermentation of wine and that their growth could be arrested by heat; and in England in the 1860's, Joseph Lister was experimenting with the use of carbolic acid as an antiseptic agent.

All records at Zurich were kept meticulously, and they furnish some of the most valuable early surgical statistics. There had been collections of statistics previously, but no one had had Billroth's courage in presenting his entire results before the tribunal of scientific criticism. In 1860, with Von Langenbeck and Gurlt, he founded the *Archiv für Klinische Chirurgie*, and in 1861, he wrote the first of his many texts; this was entitled "General Surgical Pathology and Therapeutics" (4). It is interesting that many of the concepts which Billroth enunciated in this book, nearly one hundred years ago, still apply today. For example, on the relation between surgery and internal medicine, he wrote:

"The surgeon can only judge safely and correctly the state of the patient when he is also a physician. Surgery does not consist only in operations."

In the same vein, Billroth said:

"There is some compensation for the fact that in internal medicine we must more frequently acknowledge the impotence of our treatment than is the case in surgery, although from the advances in anatomical diagnosis, we have become more certain of what we can do and what we cannot."

At Zurich, Billroth continued his love for music, and it was here that he joined a string quartet made up of professors at the University. Billroth, who was a piano virtuoso, mastered the viola in order to become a member of the quartet; and after the small musical parties, Billroth, smoking his black cigar, would resume his medical studies, which continued into the early hours of the morning. In Zurich he made the acquaintance of a young German composer and conductor who was on a concert tour. A warm friendship ensued between Theodore Billroth, the surgeon and Johannes Brahms, the composer.

In 1867, Billroth left Switzerland and accepted the chair of surgery at Vienna, a position vacated by Schuh. It is difficult to say whether he left Zurich because of sadness at the death of his child; whether he wished to be with his friend, Brahms, who had left for Vienna the previous year; or whether the new position offered increased opportunities for research and teaching. Certainly, all these factors must have been important. On the other hand, the selection of the Prussian Billroth had not been easy for the faculty of Vienna, for it was only one year after the Battle of Sadowa in which the Austrian armies were defeated by Prussia in the Seven Weeks' War. Anti-Prussian feeling ran high in Vienna and as Arpad G. Gerster wrote: "To the honor of the medical faculty, be it said, that in spite of court opposition they insisted upon their choice" (5). The faculty at that time was composed of Rokitansky, Brucke, Hebra, Skoda and Oppolzer.

Hardly settled in his new post, Billroth showed his indefatigable qualities by publishing his surgical experiences in Zurich (3). It was in Vienna, however, from 1867 until his death in 1894, that he was to earn his fame as a surgeon, as an investigator in surgical pathology, and as a bold and successful operator and teacher. In 1870, during the Franco-Prussian War, he took an active part in the field campaign and in the military hospitals of Weissenburg and Mannheim. He published numerous articles on military medicine as a result of these experiences (6). Eleven years earlier, he had demonstrated his active interest in war wounds by writing an historical essay on the treatment of gunshot injuries (7, 8). His orientation along historical and developmental patterns of surgical subjects was also sharply reflected in his frequent statement:

"Only the man who is familiar with the art and science of the past is competent to aid in its progress in the future" (2).

The earliest pioneer surgical efforts of Billroth which brought wide recognition were concerned with resection of the esophagus and larynx. It was Billroth who first extirpated the esophagus in animals (1872) and who, in 1873, first resected the human larynx (9, 10). The esophagectomy was performed in the neck and demonstrated the remarkable fact that a segment of esophagus could be removed and that healing take place in the gullet. It is little wonder that a pupil of Billroth, Mikulicz, was the first to attempt esophageal resection in the thorax some twenty-five years later.

The total laryngectomy was similarly performed after perfection of operative technique in animals and after studies of the effects of laryngectomy on swallowing and other physiological acts in these animals. The development of an improved artificial larynx by Gussenbauer, an assistant to Billroth, was another example of the care and circumspection which went into the preparation of a new operation in Vienna.

The first total laryngectomy took place on November 27, 1873; and the original publication is a milestone in surgical history (10). It must be remembered that at this time although ether and chloroform anesthesia were a little more than twenty-five years old, the principles of Listerian antisepsis were just coming into vogue. That such major resections were accomplished with crude methods of anesthesia, with no methods for replacement of blood or electrolytes, and little or no antiseptic technique, is amazing testimony to Billroth's skill as a surgeon. At Billroth's clinic, chloroform anesthesia had been used in six thousand cases up until 1870, when the preference changed to chloroform-ether (11). The laryngectomy for epidermoid carcinoma was performed with chloroform administered through a tracheotomy cannula. The patient was a vigorous, thirty-six year old male, who was a teacher of religion, and who had had hoarseness for three years and then aphonia. Postoperatively, hemorrhage occurred from the left superior laryngeal artery; this was controlled by ligation. An artificial larynx was utilized with good result, and the patient discharged three months after operation. The follow-up report of this patient is furnished by Dr. Arpad Gerster, who was later appointed to The Mount Sinai Hospital Surgical Staff (1880). Dr. Gerster wrote that in Vienna in 1874 he was fortunate to see this first patient who

was offered the cure of laryngeal cancer. "The patient wore a phonating cannula, but Professor Schroetter had discovered a relapse of cancer in the remnants of the epiglottis" (5).

Dr. Gerster, a student of Dr. Billroth, passed on a clear description of the personality of his great teacher at the height of his career:

"The temperament (of Billroth) was sedate and undemonstrative; a quiet and indomitable energy pervaded the man. His relations with the student were not those of a taskmaster and supervisor, but had the fraternal air of the older brother, full of kindness and respectful consideration."

Concerning Billroth's surgical ability, Gerster wrote:

"On familiar ground, his operative methods were rapid and summary, though always safe; but when as a pioneer, he invaded an unexplored field he was deliberate, always prepared by previous animal experiments and provided with a well-laid plan of procedure. Hemorrhage, asphyxia, or any serious accident at the operating table were always met and overcome with no flutter of excitement" (5).

Billroth's clinic in Vienna attained the pinnacle of surgical achievement in the years between 1870 and 1890, for shortly after the famous laryngeal and esophageal resections, the antiseptic principles of Lister were accepted and advanced, and the monumental work on gastric resection begun. Lister, treading knowingly in the footsteps of Pasteur and Semmelweis, enunciated his renowned doctrines in 1867 and for an antiseptic agent experimented with carbolic acid, which was being used to treat garbage in Carlisle, England (12). Although Billroth also believed and wrote that the cause of wound fever existed on the instruments and sponges, on the hands and coats of doctors and nurses, he did not at first believe that the antiseptic system rested on solid ground. As a matter of fact, after Lister in 1867 published his principles of antiseptics, Billroth was one of his severest and most outspoken critics on the continent. Billroth reduced all micro-organisms to a single species, the "cocobacteria septica" and believed that inflammation of connective tissue took place first in wound infections and then was followed by the invasion of bacteria. Furthermore, Billroth acridly wrote:

"That which of late years is often lovingly called the antiseptic treatment is in my opinion only a potential 'antiphlegmonous' or as it used commonly to be called 'antiphlogistic' treatment of wounds -which antiquated term included treatment by bleeding, low diet, purging, and all the thousand and one rational and irrational methods of combating inflammation" (2).

However, Billroth began to change his opinion about antiseptics when Robert Koch in 1877 showed for the first time that many different types of micro-organisms were capable of causing wound infection. In 1878, von Wolfer was sent to Lister's clinic; when he returned, the principles of antiseptics were adopted in Vienna. Although Billroth used carbolic acid in 1881 in his first successfu

partial gastrectomy, he repeatedly warned about its toxicity as shown by the resulting olive-green urine and by occasional fatalities. In 1879, in a letter to his assistant, Mikulicz, Billroth conceded the greatness of Lister:

"I had already been afraid that Lister was angry with me because I had not entered immediately and unconditionally upon his ideas and upon his methods. He shows himself a great man also in this, that he is so much master of his creed that he can afford quietly to wait for the judgment of others" (13).

In the 1870's, while performing the first laryngeal and esophageal resections, adopting the antiseptic system, and initiating the laboratory researches which culminated in successful gastrectomy, Billroth found the time to enrich his life with music and cultivate his friendship with Johannes Brahms and with Hanslick, the leading music critic in Vienna. Billroth lived in a house which had been frequented a century before by Haydn and Beethoven and in 1870 by Brahms (14). Through the 1870's, moreover, all chamber music written by Brahms had its first performance in Billroth's house, and all new compositions were given to Billroth in manuscript form for comment. It is said that Mrs. Billroth was always a charming hostess at the evening concerts and that at her husband's direction, champagne was served if the performance was good, but only beer if the performance was mediocre. In 1873, Brahms showed his devotion and admiration for Billroth by dedicating his first two string quartets in C minor and A minor, opus 51, to the great surgeon.

One evening in the early days of his friendship with Brahms, Billroth participated as a violinist in playing one of the composer's sextets, but because of nervousness made several errors in the reading of the music before Brahms. Billroth vividly recalled this scene in later years and remarked:

"Like an old boy, I had to undergo the bitter experience that it is foolhardy to attempt to execute anything in science or art unless one has mastered the matter in hand. I have learned never to play a piece in the presence of the composer unless it has been perfectly prepared beforehand" (2).

This attitude and the mastery of music and surgery by a drive toward perfection, stimulated William Welch, the pathologist and medical historian, to quote Landor and describe Billroth as a man "who warmed both hands before the fire of life" (14).

The scope and extent of surgery performed by Billroth before 1880 or the pre-gastrectomy era revealed his versatility as a general surgeon (11). The extirpations of the esophagus and larynx have already been described; plastic operations such as cleft lip repair, and rhinoplasty for syphilis and trauma were performed. Tumors of the thyroid gland were removed, and cysts of the thyroid gland were laid open and injected with iodine. Carcinoma of the lip and tongue were excised radically, with removal of the mandible when indicated; and the great Russian surgeon Pirogoff went to Billroth in Vienna for treatment of a carcinoma of the tongue (15). However, because of the location of the tumor and because Pirogoff was seventy years old, Billroth did not operate. Amputations of the thigh were

performed for sarcoma of the leg and nerve resections done for *tic douloureux*. Carcinomas of the rectum were excised, and carcinoma of the breast were treated by removal of the breast and axillary lymph nodes. In the days before radical mastectomy, Billroth believed that there were fewer recurrences of breast carcinoma if all the skin of the breast were excised and the wound allowed to heal secondarily. He made the observation in his book on "Surgical Pathology and Therapeutics" that in carcinoma of the breast it was difficult to compare the result of early or late operations with those in patients who ran their course without operation (4). Billroth made a plea for early referral of patients with tumors of the breast and noted that in elderly women the disease almost always ran a slower course than in young ones. Dr. Samuel D. Gross, professor of surgery at Jefferson Medical School, was so deeply impressed after visiting Billroth that he correctly predicted in his autobiography:

"What he (Billroth) may do in the way of heroic surgery, it would be difficult to foretell. Possibly his next feat may be the extirpation of the liver or of the stomach" (16).

And, in the fall of 1878, a young New York surgeon named William Stewart Halsted visited Vienna and wrote:

"What impressed me chiefly was the magnitude of the operations and the skill of Billroth and his assistants, particularly Mikulicz, and the great number of artery forceps used" (17).

Billroth is best remembered today for the first successful partial gastrectomy, performed in Vienna in 1881. At that time surgery of the stomach was not new. Gastrostomies for foreign bodies had been recorded in the early 1600's, and Merrem had studied pyloric resection in dogs in the early 19th century (18). In 1837, Egebert proposed gastrostomy for esophageal stricture, and this was successfully performed in 1846 by Sedillot for malignant stricture due to esophageal carcinoma. In 1876, sixty years after Merrem's pyloric resection, Gussenbauer and von Winiwarter in Billroth's clinic, and then Czerny and Kaiser, repeated pyloric resection in animals. On the basis of these experiments they disproved the widely-held concept that sutures in the stomach would not hold because of gastric juice corrosion (19). Furthermore, animals gained weight following pylorotomy and suffered no physiological upset as a result of removal of part of the stomach. In 1877 Billroth published a report of a successful gastrorrhaphy for persistent gastric fistula, and Gussenbauer and von Winiwarter published a statistical analysis of carcinoma of the stomach. This report, in addition to the experiments on animals paved the way for resection of gastric cancer in the human (11, 19).

The first attempt at pylorotomy was made in 1879 by Péan in France. The patient died five days after operation (20). Rydygier in 1880 also removed a carcinoma of the pylorus, and his patient died twelve hours later (21). The year 1881 marks the beginning of radical gastric surgery because in January of that year, Billroth succeeded in extirpating a cancer of the pylorus; the patient lived comfortably for four months thereafter (22).

The description of this operation merits recital. The patient, Theresa Heller, has become as famous to surgical historians as Alexis St. Martin to physiologists. She was forty-three years old and had had indigestion and tarry stools for three months. Vomiting occurred every day about one-half hour to one hour following meals, and a hard, mobile tumor of the size of a fist, was present in the umbilical region. The stomach was lavaged with fourteen litres of water on the night before the operation. An oblique incision was made in the epigastrium over the tumor from right to left. Double ligatures were used to divide the lesser and greater omentum, and enlarged lymph nodes were found in the gastro-colic ligament. The tumor was excised with the distal portion of the stomach. The cut end of the stomach was closed from below upward, starting on the greater curvature, with twenty-one sutures, some deep and some superficial. The duodenum and stomach were then united on the lesser curvature with 33 silk sutures. The stomach was sponged with 2% carbolic acid, and the abdomen closed without drainage. The entire operation had lasted one and one-half hours; and pathological examination revealed the lesion to be alveolar carcinoma of the pylorus with no involvement of lymph nodes. It is curious that Rokitsansky, the pathologist at Vienna, was convinced that pyloric cancer scarcely ever extended to the duodenum (11). We now know that this is not true and that pyloric carcinoma may often show submucosal extension into the duodenum.

Theresa Heller did well after operation, had ice, acid milk, and then gradually increasing amounts of coffee and tea. The sutures were removed on the sixth day and the wound healed per primam. Wine enemas were given for nutrition for the first thirteen days. On the twentieth day, the patient ate cutlets and then beefsteak.

Billroth's second pylorectomy was not so successful. In this instance, the stomach was greatly dilated; after operation the patient vomited large amounts of bilious fluid. Re-exploration was performed on the seventh day and a tube placed in the duodenum for feeding. On the next day, the patient died. Autopsy showed that the closed-over greater curvature of the stomach had developed into a pouch in which food and secretions had collected. This finding proved important in the evolution of gastric surgery.

In the third case the method of anastomosis was modified, and the stomach was divided obliquely. The duodenum was attached to the greater curvature of the stomach to prevent the formation of a pouch (Fig. 2).

Thus, the so-called Billroth I partial gastrectomy was discovered and improved after systematic animal research, statistical analysis, and clinical experience. Six months later on September 28, 1881, von Wolfler, an assistant of Billroth, encountered an orange-sized carcinoma of the pylorus which had infiltrated the hepatoduodenal ligament and pancreas and was therefore deemed inoperable (23). At Nicoladoni's suggestion, a loop of jejunum was brought up and anastomosed to the stomach thereby restoring gastrointestinal continuity, which had been interrupted by the obstructing carcinoma. Gastroenterostomy thus came into being; and the patient obtained palliation of his obstructive symptoms.

In 1885, Billroth, during a pyloric resection for cancer, found that he had removed so much of the stomach that he could not unite the stomach and duo-



FIG. 2. The Development of the Billroth I Operation, from Billroth's "Clinical Surgery." Figures 1-5 show the steps in the anastomosis between the duodenum and the lesser curvature of the stomach after pylorotomy. The closed-over greater curvature of the stomach acted as a pouch which retained food and secretions, and the method of anastomosis was revised. Figures 6-7 demonstrate the present-day type of anastomosis between duodenum and greater curvature of the stomach as developed by Billroth. Figures 8-11 illustrate a variation in gastroduodenostomy.

denum. He closed the duodenum as a blind pouch and anastomosed the stomach and jejunum. Thus, the Billroth II gastric operation was invented.

It is interesting that in the final analysis of cases of partial gastrectomy for carcinoma, the two cases of Billroth II operation are referred to as the atypical resections, whereas the Billroth I cases are called "typical resections" (24). The gastroenterostomies were usually retrocolic, less often antecolic. In the series of cases reported from 1885 to 1889, the mortality is understandably high—six operative deaths in ten cases of Billroth I partial gastrectomy and six deaths in 11 cases of gastroenterostomy. In the statistical analysis, a case of gastroenterostomy performed by an assistant is listed, and the cause of the patient's demise frankly stated in the autopsy report that "die Arterie hepatica ist ligirt."

The pioneering efforts did not cease or decelerate after gastrectomy, for in November, 1882, at Billroth's clinic, von Winiwarter performed the first cholecystenterostomy, and Langenbuch did the first cholecystectomy. Mikulicz sutured a perforated gastric ulcer in 1883; and in 1886 Heineke and Mikulicz independently performed pyloroplasty for benign stricture of the pylorus due to ulcer.

Intestinal surgery gained impetus in Vienna during the 1880's. Billroth was the first to resect the cecum. Rectal carcinoma was removed with preservation of the anus in seven cases and with the establishment of a sacral colostomy in eight cases from 1878 to 1890. In all operations, Billroth's doctrine in the days of high operative mortality was as follows:

"One should operate only when there are several chances of success; to operate without a chance means to prostitute the exalted art and science of surgery and make it dubious in the minds of the laity and colleagues. But where is the measure according to which the chance of success can be gauged? It lies in the untiring study of our science, in the acute criticism of our own observations as well as the observation of others, in the minutest examination of each case and in the critical evaluation of our experiences" (2).

By 1890, abdominal surgery had become recognized and widely practiced throughout the civilized world after the fundamental clinical and experimental contributions of Billroth and his associates.

In the latter part of their lives, Billroth and Brahms had differences and disagreements. Billroth praised the music of the French composer, Massenet; Brahms disliked it. One evening, in Billroth's house, Brahms found that the first line of the manuscript of his A minor quartet, which he had dedicated and presented to Billroth had been cut out and mounted with one of his own photographs. This angered Brahms greatly (25, 26). Billroth died in 1894 of heart disease; Brahms died three years later of jaundice attributed to carcinoma of the liver. After Billroth's death, the great Viennese critic, Hanslick compiled a literary work which he had encouraged Dr. Billroth to undertake on the physiology of music, entitled "*Wer ist Musikalisch?*" (27). It is unfortunate that although Theodore Billroth wrote several musical compositions, he thought none good enough for posterity and destroyed the manuscripts.

Billroth's life, viewed in perspective, is that of a man of inexhaustible energy with a keen ability for leading and inspiring young men, and an innate talent which has been compared to the attribute of Phoebus-Apollo, the Greek god of both medicine and music (14).

The Nineteenth Century is famous for the beginning of anesthesia and antiseptics, and for the birth of abdominal surgery. No one man is more responsible for laying the groundwork of abdominal surgery than is Theodore Billroth; and with Czerny, Gussenbauer, von Winiwarter, Mikulicz, von Wolfer, Gersuny, and many others, the school of Billroth was perpetuated and is still alive today. Theodore Billroth, who was at all times modest and completely devoid of vanity, hardly appreciated the everlasting influence which he and his students would exert on future generations of surgeons. Late in life he wrote:

"What gave me the greatest satisfaction in my long life was to have founded a school which continues my work in its scientific as well as its humanitarian aspect, and will make it last for a while" (2).

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DR. RICHARD LEWISOHN

I was Assistant for 2½ years (1904-1906) to Professor Vincenz Czerny in Heidelberg, one of Billroth's assistants, before Czerny was called to the chair of

surgery in Freiburg and later to Heidelberg. Thus, I was brought up, though indirectly, in the atmosphere of the Billroth Clinic.

Billroth was 31 years old when he was called to the University of Zurich. A few years later he was called to Vienna, in those days one of the greatest and best-known universities in Europe. As a young man he published with his pupil Winiwarter a book called *Surgical Pathology and Therapy*. It appeared in 12 editions and was considered a "must" on every surgeon's book shelf. This great work has been translated into the languages of nearly all civilized countries.

Another great book published by Billroth was translated into English thirty years after Billroth's death by William Welch, the great founder of the Department of Pathology at Johns Hopkins University. It is entitled *The Medical Sciences in the German Universities, A Study in the History of Civilization*. This book may be considered a forerunner to Abraham Flexner's great book in which he presented many years later his directions for the improvement of teaching at our American universities.

Billroth's great and many-sided contributions to the field of Surgery have been discussed very vividly by Dr. Mandelbaum. To enumerate them again would simply mean repetition. The so-called Billroth I and Billroth II techniques for gastric resection have made his name a household word among young and old surgeons.

Like all great men, Billroth showed great talent, not only in his chosen field of activity, i.e. surgery, but along other artistic lines. He was not only a lover of music, he was a great musician. One of his closest friends was Johannes Brahms. His letters to Brahms are a classic, discussing a wide field of musical endeavor (compositions, piano techniques, etc.) His correspondence with Hanslick, the leading music critic in Vienna in Billroth's day, also makes interesting reading.

It has been said very often that Billroth selected his assistants, not only for their surgical, but just as much for their musical talent. However that may be, I know that my teacher Czerny was an excellent pianist. Another former assistant, the great surgeon Mikulicz, was a master musician.

Billroth's position in the surgical world was unique. Whenever a vacancy occurred at a university in Germany, Austria, or Switzerland, the faculty simply wrote to Billroth for advice, asking him who should be their next professor of surgery. His advice practically amounted to a nomination for that position. Thus Billroth placed his assistants all over Europe.

I cannot close this brief discussion of "Billroth, the Surgeon and the Man" without referring to the close relationship between Billroth and his assistants. He kept in constant contact with them by letters and through occasional visits long after they had left his clinic. The voluminous correspondence with his assistants was published after his death in a volume *Billroths Briefe*. The 9th edition of this charming book appeared in 1922, nearly 30 years after his death.

We can say without exaggeration - Billroth was a giant. His memory will live as long as surgery lives.

THE ADVANTAGES OF COBALT-60 IN THE PRACTICE OF RADIOTHERAPY*†

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With more than two and one-half years of experience with a hectocurie cobalt teletherapy unit in private office practice, the authors are convinced that cobalt-60 teletherapy has superseded 200 Kv x-ray in general radiotherapeutic practice.

The cobalt-60 teletherapy unit used by us was designed by the Medical Division of the Oak Ridge Institute of Nuclear Studies of which Dr. Marshall Brucer is chairman. It was on the basis of the practicability and potential popularity of such a hectocurie model that the Oak Ridge Institute of Nuclear Studies was able to expedite the production and availability of radioactive cobalt units at Oak Ridge.

Cobalt-60 is the radioactive isotope produced in the reactor by neutron bombardment of ordinary metallic cobalt-59. It has a half-life of 5.3 years and disintegrates to nickel-60 with the emission of two gamma rays, 1.13 and 1.31 Mev, equivalent to the average radiation produced by a 3 million volt x-ray machine. The specific activity of cobalt-60 can be made high enough to concentrate sources up to 3000 curies in a disc of 2 cm. diameter. Most of the teletherapy sources in use today range from 300 to 1500 curies, corresponding to an output of 400 to 2000 roentgens per hour at 1 meter (rh_m). This output range is within the limits of usefulness in practical radiation therapy. The kilocurie sources are contained in large machines which require relatively elaborate and costly housing, but the hectocurie sources can be placed in units that are of the same size as 200 Kv x-ray machines.

THE HECTO CURIE UNIT

Our hectocurie unit (fig. 1) consists of a cobalt-60 source head mounted on an upright floor stand. The source head is a 50 cm. diameter lead filled spherical shield with a snout-like projection that has an aperture for the gamma ray beam. It can be raised or lowered on the vertical stand and the gamma ray beam can be directed at any angle within a 90 degree arc from horizontal to vertical. The cobalt-60 source is on the circumference of a tungsten wheel within the head and the wheel rotates the radioactive cobalt to the aperture when the machine is "on." In the "off" position the radioactive source is near the geometric center of the lead protective sphere. Treatment fields are defined by heavy brass cones inserted into the aperture. The distance from the source to the end of the cone

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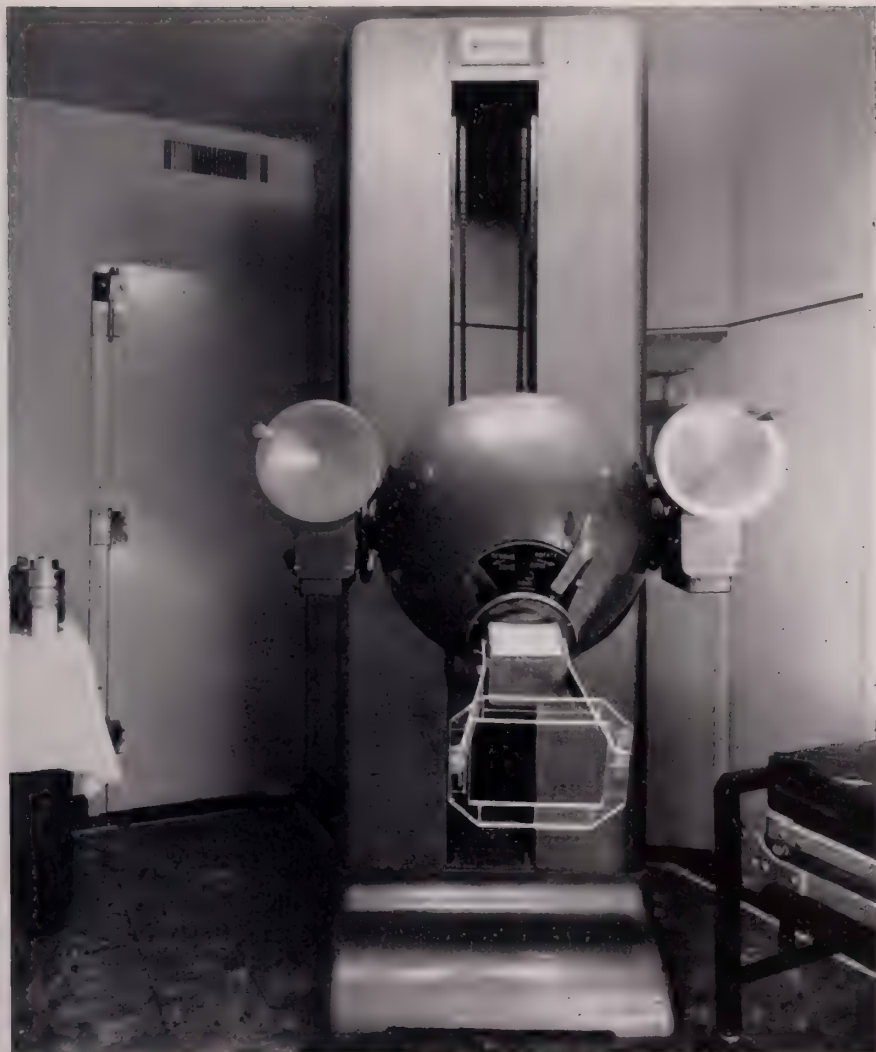


FIG. 1

is 30 cm. and special attachments are used for longer distances with corresponding increases in field sizes. Modifications of the standard square, rectangular, or circular fields are made by means of lead blocks of appropriate size and shape. A lead thickness of 5 cm. is equivalent to 4 half value layers which reduce the incident beam to 6 per cent of its original intensity.

RADIATION PROTECTION

All persons outside the treatment room are protected from direct and scattered radiation by lead and concrete shielding in accordance with the recommendations in handbook 54 of the United States Bureau of Standards. The cost and

weight of this shielding were kept to a minimum by limitation of the useful beam to actual requirements for treatment and by its direction into a corner of the room toward a relatively unoccupied area. Adequate protection for leakage and scatter radiation was provided by approximately 1 cm. of lead on the walls. Details of protection for this unit may be seen in Braestrup's publication in *Radiology*, December 1955 (2).

The control panel is relatively simple and consists of a time clock, which is the only setting required, an "on and off" switch, and safety light indicators. The viewing window is situated behind the hectocurie unit and a good view of the patient and the therapy room is obtained by means of a large reflecting mirror on the opposite wall. The lead counterweights in the upright columns are strategically located as an effective barrier for scatter radiation directed backwards so that a lead glass panel equivalent to 3 mm. of lead is adequate for the viewing window.

ADVANTAGES OF COBALT-60 TELETHERAPY

From our own studies and clinical experience and from the reported experiences of others (3-9), we have observed that cobalt-60 teletherapy possesses several important advantages over treatment with 200 Kv radiation and these advantageous features may be listed as follows:

1. Increased depth dose
2. Decreased bone absorption
3. Increased tolerance of skin
4. Simplified techniques of treatment
5. Decreased radiation sickness
6. Dependability

A further advantage peculiar to the hectocurie unit is the short source-skin distance, which is desirable for the more superficially situated tumors.

Increased Depth Dose

The increase in depth dose is appreciable. When the source-skin distance with cobalt-60 is 35 cm., the depth doses are approximately those of 200 Kv rays at 80 cm. target-skin distance. When cobalt-60 is used at 50 cm. source-skin distance, the depth dose is greater than can practically be achieved by 200 Kv x-rays. There is also less side scatter with cobalt-60 radiation, although this advantage over 200 Kv x-rays is somewhat offset by the relatively wide geometric penumbra.

Decreased Bone Absorption

The absorption of 200 Kv radiation energy is several times higher in bone than it is in soft tissues, resulting in an appreciable reduction in depth dose and a greater radiation effect in the bone itself. With cobalt-60 radiation the energy absorption in bone is approximately the same as it is in soft tissues. Therefore in contrast to 200 Kv x-rays there is with cobalt-60 gamma rays no decrease in depth dose due to bone in those anatomical regions where bone must be traversed

by radiation, such as the brain, pharynx, spine, and pelvis. Radionecrosis of bone should be less frequent and we have not experienced it at all in patients treated thus far.

Increased Tolerance of Skin

The increased tolerance of the skin is the most obvious advantage of cobalt-60 teletherapy. Doses of the order of 6000 to 7000 roentgens in 6 weeks produce only a mild degree of erythema and pigmentation. Skin reactions are no longer deterrents to any treatment plan. The maximum dose occurs not on the surface of the skin but a depth of 5 mm. where equilibrium is reached between primary and secondary radiation. The actual dose at the skin surface may be less than half of this maximum. Thus it is impractical to describe "skin" dose with cobalt-60 radiation. It is more useful to indicate the "air" dose at the skin surface and the "tissue" dose in depth. In order to take full advantage of the skin-sparing effect of cobalt-60 radiation, bolus should not be used and surgical dressings in the treatment field should be removed.

Simplified Techniques of Treatment

The increased depth dose, the decreased bone absorption, and the increased tolerance of the skin, combine to a further advantage for cobalt-60 teletherapy, which is simplification of treatment techniques. More effective treatment with fewer fields is possible for most tumors, while with 200 Kv x-rays the higher doses in depth can be achieved only by an increase in the number of treatment portals or by rotation therapy, methods which are cumbersome in general and inapplicable in superficial tumors.

The superficial tumors, such as those located in the peripheral lymph nodes, thyroid gland, parotid gland, middle ear, maxillary antrum, mandible, chest wall, and abdominal wall, which are irradiated through a single field, are more easily treated to cancerocidal doses with cobalt-60 radiation than with 200 Kv x-rays. The skin reactions with 200 Kv x-rays at dose levels higher than 4000 roentgens are usually so intense that no further treatment can be given while with cobalt-60 doses of 6000 to 7500 roentgens can be safely administered over a period of 6 weeks with a relatively mild skin reaction characterized by dry desquamation and pigmentation.

For most tumors treated with cobalt-60 a dose of 6000 to 7000 roentgens is administered over a period of 5 to 6 weeks. The number of fields required depends upon the proximity of the tumor to the surface and its accessibility. In general, the treatment plans with cobalt-60 are similar to those with 200 Kv except that a smaller number of fields may be adequate. With cobalt-60 greater precautions are necessary for the protection of uninvolved vital structures. With 200 Kv x-rays the skin reactions have been safeguards against overdosage, but with cobalt-60 the radiotherapist must rely upon the known limits of radiation tolerance of the various structures irradiated. The dose received by each structure must be estimated prior to its administration, and these structures may be protected by accurate field definition and proper beam direction. In the region

of the eye a properly supported block of lead 5 cm. thick protects the conjunctiva and lens from the direct beam and the penumbra radiation. In the region of the spine, irreparable injury to the spinal cord may be avoided by keeping the dose to this structure below 5000 roentgens in 5 weeks. The tolerance of the intestinal tract is of the same order of magnitude. While treatment techniques may be simplified with cobalt-60 teletherapy, attention to details is essential both for the tumor dose and for the protection of normal uninvolved structures.

Decreased Radiation Sickness

Radiation sickness seems to be somewhat less severe in the patients treated with cobalt-60 radiation than in those treated with 200 Kv x-rays. It is difficult to assess the degree of radiation sickness because of the large personal factor but patients tolerate abdominal fields and hepatic radiation with less complaints, and larger doses can therefore be given with less morbidity. One explanation for the decreased radiation sickness with cobalt-60 is the decreased side scattered radiation and the more accurate definition of the volume of tissue that is to be irradiated.

Dependability

Another advantageous characteristic of the cobalt-60 hectocurie teletherapy unit over the 200 Kv x-ray machine is its dependability, a feature due to the simplicity of the apparatus. At no time has our cobalt unit been out of commission, and no repair service has been required. This experience is in marked contrast with the many service calls and several breakdowns during the same period for the 200 Kv x-ray apparatus in the adjacent room.

CLINICAL EXPERIENCE

Since our cobalt-60 hectocurie unit has been in use we have employed it in the treatment of nearly every case of cancer that previously would have been treated with 200 Kv x-rays. Our experience is not long enough to establish comparative cure rates but we have enough experience now to determine the range of applicability of cobalt-60 radiation, the reactions of the patient, and the early results of treatment.

Head and Neck Cancer

Tumors of the head and neck are particularly suitable for treatment with cobalt-60 radiation, and it was for this region of the body that our hectocurie unit was originally designed. Cancer of the nasopharynx, nasal cavity, and paranasal sinuses, of the mouth, tonsil, oropharynx, larynx, and laryngo-pharynx, of the salivary glands, and metastatic cancer in the lymph nodes of the neck are easily treated to doses of 6000 roentgens or higher in 5 to 6 weeks. The skin reactions are minimal and the risk of osteo-radionecrosis is greatly reduced. Similar doses with 200 Kv x-ray therapy would entail intensely severe reactions.

Cancer of the larynx is now treated with cobalt-60 radiation by a method based upon the 200 Kv x-ray technique of Harris, Silverstone, and Kramer. Radiation

is directed through two opposing lateral fields to an exposure dose of 5000 roentgens on each side in 6 weeks with a tumor dose of approximately 6500 roentgens. While it is premature to discuss comparative cure rates, certain observations are worthy of comment. The early favorable response is the gradual disappearance of the neoplasm during the course of therapy. Membrane reactions within the larynx and the moderate edema of the arytenoids so often seen after 200 Kv x-ray treatment are less frequently encountered with cobalt-60 teletherapy. The most striking advantage, however, is observed in the skin reactions, which are slight and which heal to a practically normal appearance, never reaching the stage of moist desquamation that usually follows similar treatment with 200 Kv x-rays. Telangiectasis and atrophy have not been seen in patients treated over two years ago.

Some laryngological surgeons believe that cobalt-60 irradiation causes marked subcutaneous vascular changes which preclude healing of laryngectomy or neck dissection wounds. However, several of our patients have been subjected to such operations after cobalt-60 irradiation and have healed satisfactorily. Since very high doses can be given to a single field with cobalt-60 radiation because of the slight skin reactions, it is to be expected that injudicious overdosage may be followed by breakdown of surgical wounds more often in patients treated with cobalt-60 than in those treated with 200 Kv x-rays.

Cancer of the thyroid can be treated with doses of 6000 roentgens in 5 or 6 weeks through a single portal without developing a skin reaction more marked than a mild degree of pigmentation. The underlying tissues are soft and supple, whereas with 200 Kv x-rays, the maximum safe dose to the thyroid region of the neck is about two-thirds of the dose with cobalt-60, and it causes severe skin and subcutaneous changes.

Our present experience with cobalt-60 teletherapy of head and neck cancer indicates that more cases are amenable to treatment than previously and that the curable cases will be cured with much less radiation morbidity while the advanced cases can profit from a greater degree of palliation.

Brain and Pituitary Neoplasms

In the treatment of brain tumors, the optimum dosage has not been established. The favorable results of radiation therapy for brain and pituitary neoplasms have been generally limited to temporary regression of growth and alleviation of symptoms. There is no clinically noticeable difference in the biological effectiveness of 200 Kv x-rays or cobalt-60 radiation. In most cases, however, re-operation or re-irradiation or both are sooner or later required. The skin-sparing effect and diminished bone absorption of cobalt-60 radiation not only permit more efficient irradiation of brain tumors to higher doses but also allow repetition of the complete course of therapy when indicated. Neurosurgeons should be able to operate after cobalt-60 teletherapy, if necessary, with less risk of wound breakdown. The advantages of cobalt-60 teletherapy are of particular importance in pituitary neoplasms for which either post-radiation surgery or re-treatment by irradiation is fairly common and the results are satisfactory.

Breast Cancer

With cancer of the breast, the radiotherapeutic problem is not with the primary tumor, which is best managed surgically, but with the regional lymph nodes and the distant metastases. Post-operative radiation therapy for cancer of the breast is directed to the lymph nodes at the apex of the axilla, in the supraclavicular fossa, and along the internal mammary vessels. These are the common sites of regional spread of this disease. With cobalt-60 teletherapy a dose of 4000 roentgens can be administered to these lymph nodes through a single portal in each region with minimal skin reactions characterized by slight scaling and slight pigmentation. The same dose with 200 Kv x-rays causes a very severe reaction which is painful and disabling and is often followed by marked atrophy and telangiectasia. The important chain of lymph nodes along the internal mammary vessels have presented a challenge to the radiotherapist with 200 Kv x-rays because the dose to these relatively superficial nodes is limited by the tolerance of the skin and the "shadow" effect of the ribs. Neither of these limitations, however, affect the administration of a high dose with cobalt-60 radiation through a single portal over the sternum and adjacent costal cartilages. Doses up to 6000 roentgens have been administered to the supraclavicular fossa, axilla, and parasternal area.

Irradiation of the chest wall can be effectively accomplished with a tangential technique by which high dosage is attained in the chest wall but the underlying lung parenchyma may be relatively spared. In the treatment of distant metastases, particularly those in bone, equally good results may be obtained with 200 Kv x-rays or cobalt-60 radiation but if repetition of the radiation is required, cobalt-60 teletherapy is the method of choice because of its skin-sparing advantage.

Cancer of the Lung and Esophagus

The effectiveness of radiation therapy in cancer of the lung and cancer of the esophagus is limited to the primary tumor and adjacent lymph node involvement in which regression of the neoplasm may be achieved. Sometimes this regression appears complete as indicated by the roentgenological disappearance of the mass in the lung or by roentgenological restoration of the lumen of the esophagus in an examination with barium. More often than not, however, the regression of the tumor is temporary or partial. After a variable period of time, the tumor recurs or spread of the tumor beyond the original treatment area is observed. In spite of this morbid outlook, however, all cases in which the primary tumor and its adjacent lymph node metastases can be encompassed within a single reasonably-sized volume of tissue should be irradiated if complete surgical removal is not possible. A tumor dose of 5000 to 6000 roentgens in 6 weeks can be administered with cobalt-60 teletherapy with relatively little discomfort to the patient. Relief of the superior vena cava compression syndrome can also be frequently effected favorably. Skin reactions are no longer a problem as with 200 Kv x-rays and since higher doses can be given to each field, fewer fields are required with cobalt-60. The spinal cord can be protected by proper planning

of the radiation program. Radiation fibrosis of the lungs can be held to a minimum by the selection of treatment fields which include only the minimal amount of lung tissue consistent with adequate coverage of the malignant tumor. With precision methods of tumor localization, such treatment planning is possible.

Malignant Neoplasms of the Stomach and Upper Abdomen

The malignant neoplasms in the upper abdomen are generally inoperable and incurable with only a few exceptions. The diagnosis is usually established by surgical exploration. The pain and dysphagia of inoperable or recurrent cancer of the stomach may sometimes be relieved by radiation therapy. Temporary relief of obstruction due to recurrent neoplasm at the gastro-esophageal anastomosis can sometimes be obtained with doses of 5000 to 6000 roentgens. The important field for radiation therapy in the upper abdomen, however, is the tumor mass that is found to be lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoblastoma, Hodgkin's Disease, or neuroblastoma, all of which are highly radiosensitive and may be eliminated locally by doses of the order of 3000 to 4000 roentgens. Some of the rarer retro-peritoneal sarcomas may require higher doses.

Cancer of the Colon

Not infrequently cancer of the colon may be locally advanced and adherent to the anterior or posterior abdominal wall. Surgical removal is either incomplete or not possible and radiation therapy may be directed to the region of the mass for its local effect in reducing the size of the tumor. With accurate localization, as established by fluoroscopic examination, it is possible to direct a large dose of radiation, 5000 to 7000 roentgens, to the primary tumor, if inoperable, for the purpose of improving the lumen and obviating the need for a colostomy. Metastases that are scattered throughout the peritoneal cavity or liver are not suitable for treatment by any form of irradiation, but those forming a single well delineated mass can often be effectively treated.

Cancer of the Rectum

The bleeding, pain, and purulent discharge of an inoperable cancer of the rectum are not relieved by colostomy but can at times be effectively controlled by radiation in the dosage range of 3000 to 5000 roentgens. This radiation must be directed to the malignant neoplasm through sacro-coccygeal and buttock fields. The skin-sparing advantage of cobalt-60 radiation is especially welcome to these patients who are already miserable with rectal symptoms and who could not tolerate the radiodermatitis of 200 Kv x-rays administered in doses high enough to affect the tumor. After abdomino-perineal resection, a common site of recurrence is either in the sacro-coccygeal hollow or in the region of the colostomy. Doses of the order of 4000 to 6000 roentgens are frequently effective. For such high doses both sites are best treated with cobalt-60 radiation in order to avoid a skin reaction which would be very disturbing to a patient already burdened by a colostomy.

Cancer of the Bladder

With cobalt-60 teletherapy, tumor doses of 6000 to 7000 roentgens can be administered to the bladder over a period of 6 to 7 weeks. The skin reactions are minimal and would not interfere with any subsequent surgery should that become necessary. The same dose administered with 200 Kv x-rays would necessitate an intense skin reaction of the treated areas which include the suprapubic region, both buttocks and sacro-coccygeal area. Radiation cystitis is produced by either method but the patients appear to tolerate cobalt-60 teletherapy with less discomfort, probably because they do not have to suffer from radiodermatitis at the same time. While it is too early to evaluate the effect of cobalt-60 teletherapy on cancer of the bladder, this treatment appears to be somewhat more satisfactory than similar treatment with 200 Kv x-rays.

Cancer of the Ovary

Cancer of the ovary tends to spread widely over the peritoneal cavity and it is therefore necessary to treat almost all of the peritoneum. In the very early stages the metastatic spread may be limited to the pelvis and lower abdomen. Because of the large volume of tissue that must be irradiated, the tumor dose is limited to 3000 or 3500 roentgens. Such a dose with cobalt-60 teletherapy produces practically no reaction on the skin and radiation sickness appears to be less than with the equivalent dose administered with 200 Kv x-rays. This dose can be repeated, if required, without significant effects on the skin. If a favorable effect is obtained with the initial course of radiation therapy, repetition of the treatment is desirable at the first sign of recurrence.

Cancer of the Cervix and Corpus Uteri

In the treatment of cancer of the cervix or of cancer of the corpus uteri with radium, it is possible in most instances to administer a dose in excess of 6000 roentgens to the endometrial cavity, lower uterine segment, cervix, vagina, and paracervical triangles, but the dose to the lateral pelvic wall seldom exceeds 2000 or 2500 roentgens with radium alone. Supplementary radiation is therefore required and can be administered to a dose of 3000 roentgens with 200 Kv x-rays if the patient is not obese. Higher supplementary doses up to 5000 or 6000 roentgens are often required for stage III and advanced stage II cases and can be administered with cobalt-60 radiation with relatively little skin reaction. The limiting factor is the tolerance of the intestines that must of necessity be included within the radiation field. In very advanced cases it may be necessary to treat large tumor masses with external radiation alone to a dose above 5000 roentgens. This cannot be done with 200 Kv x-rays without producing a severe radiation morbidity and in such cases cobalt-60 radiation is clearly indicated.

Malignant Tumors of the Testis

Seminoma and other malignant tumors of the testis are generally treated by orchidectomy followed by irradiation of the inguino-iliac and abdominal aortic lymph nodes. For a dose of 2500 to 3000 roentgens to these nodes, which is prob-

ably the safe minimum effective dose for metastases from seminoma, skin doses of 3000 to 4000 roentgens must be administered over large areas of the pelvis, abdomen, buttock, and dorso-lumbar region. While this can be done with 200 Kv x-rays, the ultimate effect on the skin is a reaction of moderate severity which may in later years lead to atrophy, telangiectasia, and other manifestations of skin damage. With cobalt-60 radiation the same tumor dose can be administered with very slight or no skin reaction. Higher doses can be safely given for the more radio-resistant tumors such as the malignant teratomas. Since the cure rate for seminoma is high and the disease is predominant in young adults, the skin-sparing effect of cobalt-60 radiation is highly to be desired.

Malignant Lymphoma

Lymphosarcoma, giant follicular lymphoblastoma, and Hodgkin's Disease respond well to doses in the range from 600 to 3000 roentgens. In the peripheral lymph node areas these doses can be administered equally well with either 200 Kv x-rays or cobalt-60 radiation, but for the lesions deeply situated in the chest or abdomen, cobalt-60 radiation is preferable because of its better depth dose. Recurrences in the peripheral lymph node areas are preferably treated with cobalt-60 radiation in order to avoid unfavorable skin reactions. Since malignant lymphomas occur in children and young individuals as well as adults with survival times often exceeding 5 years and sometimes 10 years, the long range effect of radiation on the skin would favor the use of cobalt-60 radiation if a choice were available.

Metastatic Disease

Metastatic deposits usually require as high a dose as the primary neoplasm for their control or eradication. Metastatic disease in the lymph nodes represents a major challenge to both the surgeon and the radiotherapist. With 200 Kv x-rays the intense skin reaction of high doses limits the usefulness of this quality of radiation only to relatively small areas that can tolerate high dosage. With cobalt-60 radiation, the potentialities of control of metastatic lymph nodes are appreciably increased because much larger areas can be treated to high dosage. For this purpose the short source-skin distance of the hectocurie unit is a useful advantage in combining high dosage near the surface with sparing of the skin. Metastatic deposits in the bones, skin, lungs, and other viscera are treated only if they produce symptoms which could not be relieved by simpler measures and only if the treatment itself does not introduce undesirable complications. The choice of 200 Kv x-rays or cobalt-60 radiation depends upon the size of the dose required and an estimation of the reactions such a dose might produce.

DISCUSSION

The major technical problems of radiation therapy are based upon the need for higher doses in depth with sparing of the skin. With 200 Kv x-rays, technical improvements have been effected by means of the grid technique, the use of multiple ports, rotation therapy, and the use of higher filtration and longer

target-skin distances. While all of these special techniques greatly improve the administration of 200 Kv x-rays, these improvements are exceeded by the advantages of cobalt-60 radiation which has a higher depth dose, greater skin tolerance, less bone absorption, and simpler techniques of administration. If the special techniques designed for the improved administration of 200 Kv x-rays are applied to cobalt-60 radiation there would be still further improvement which, however, is seldom needed except for special problems.

A new problem introduced by cobalt-60 radiation and not present with 200 Kv x-ray machines is that of protection from radiation that is very highly penetrating and is constantly present. Unlike an x-ray machine, cobalt-60 radiation cannot be turned on or off. It is present all the time. To be turned "off" it must be shielded by thicknesses of heavy metals such as lead, tungsten, mercury, or uranium. This shielding also introduces a weight problem and the need for stronger mechanical supports. All of these problems have been adequately solved and cobalt-60 apparatus can now be installed in most locations with proper safety for all individuals.

There is a small group of malignant neoplasms that can be better managed with x-rays in the 45 to 250 Kv range than with cobalt-60 teletherapy. In the treatment of cancer of the skin, eyelids, and lip, the technical problem is not skin sparing and not high depth dosage but, instead, high surface dose with relatively little depth dose. The better method of treatment for these lesions is superficial x-ray therapy. A similar technical problem exists with certain small growths that are so favorably located on the buccal mucosa, palate, tonsil, or tongue that they can be well encompassed by an intra-oral x-ray treatment cone and therefore managed directly by intra-oral x-ray therapy without the need of traversing normal skin or other normal structures.

Our discussion of the relative value of cobalt-60 radiation and 200 Kv x-rays does not apply to radium therapy. The gamma radiation of radium is qualitatively similar to that of cobalt-60 and its use in the form of surface plaques, implants, or intra-cavitary applicators does not conflict with cobalt-60 teletherapy. It is the radium bomb which is being replaced by cobalt-60 because cobalt-60 is now available in far greater quantities and activities than radium. The largest radium bomb in the world has only 50 curies whereas cobalt-60 sources exceeding 1500 curies are common and some have more than 2000 curies.

With the few exceptions that have been discussed, the advantages of cobalt-60 teletherapy over 200 Kv x-ray therapy apply throughout the general field of radiotherapy. Again with the few exceptions mentioned, whatever can be done with 200 Kv x-rays can be done better with cobalt-60 teletherapy. Higher doses can be administered with much greater safety to all tumors, superficially or deeply situated. Many of the superficially located tumors that could not be adequately treated with 200 Kv x-rays can be given cancerocidal doses with cobalt-60 radiation through a single treatment field. This feature of cobalt-60 radiation is illustrated by a case of carcinoma of the middle ear which was treated with a tumor dose of 6000 roentgens administered through a single field. The pinna which was included within this field received the high exposure dose

of 6900 roentgens but the reaction was mild, it healed to a normal appearance, and the patient has been free of disease for over two years. Another illustration is a case of chordoma of the sacrum, which was found to be inoperable on surgical exploration because of neoplastic infiltration of the buttock muscles. It was treated one and one half years ago through a single direct field with a tumor dose of 6000 roentgens, following which the tumor was no longer palpable. The reaction of the skin over the sacro-coccygeal area was one of a moderate degree of pigmentation. Similarly, a patient with squamous cell carcinoma of the anus was treated with an exposure dose of 6000 roentgens administered directly to the anus. There was a mild easily tolerated reaction that never at any time incapacitated the patient who is free of disease with a normal appearing and normal functioning anus for over one year. A recent case of a highly malignant neurogenic tumor of the perineal body, extending from rectum to vagina in a young girl, was treated with cobalt-60 radiation through a direct field over the tumor. It was necessary to include both the rectum and the vagina in the treatment field. A dose of 6000 roentgens caused rapid disappearance of this tumor with some pigmentation of the treated area and very slight rectal discomfort. The patient was ambulatory during the entire course of therapy and attended school. The cases just cited could not have been treated to the same dosage with 200 Kv x-rays. The skin reactions would have been too severe, even with much less dosage, and the patients would have suffered severely. Therefore, in addition to its technical and qualitative advantages, cobalt-60 teletherapy has the further advantage of increased range of usefulness in the treatment of malignant disease.

CONCLUSIONS

In the light of our own experience and of the rapidly accumulating literature, it is evident that cobalt-60 radiation is superior to 200 Kv x-rays in the radiation therapy of malignant disease. The few exceptions only emphasize the particular advantages of cobalt-60 radiation over 200 Kv x-rays. Radiation morbidity is reduced with cobalt-60 radiation, and patients can be spared much suffering due to radiation reactions. The favorable effects of radiation therapy can be appreciably improved. In the general practice of radiotherapy today, cobalt-60 teletherapy has superseded 200 Kv x-ray therapy.

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ELECTROMYOGRAPHY AS A TOOL OF CLINICAL NEUROPHYSIOLOGY

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The electrical activity associated with muscular contraction and the initiation of contraction by the application of a changing potential are among the oldest observations in modern physiology. It was the observation of contraction when dissimilar metals were placed on a muscle that led Volta to his subsequent investigation and eventual creation of the voltaic pile or battery. Throughout the twentieth century, as electricity became a more convenient tool to manipulate, observations of the electrical activity associated with living systems (not only of muscles but of the surface of cells and within cells) became an increasingly popular and widely used technique. With the technological advances of the twentieth century providing recording systems of low inertia, the utility of electrical methods of investigation expanded widely. The use of the tools of electronics for the purpose of acquiring information as to the function of various systems in the body became an everyday approach for physiologists and, later, clinicians. Thus we have witnessed the development of electrocardiography, electroencephalography and corneo-retinal potential recording. When these tools are applied to the study of muscle function we have electromyography.

Perhaps one of the largest defects in classical electromyography, as evidenced by the reports in the literature, has been the emphasis on the muscle in isolation from its nervous system attachments. Studies of muscle function have been accomplished by recording the irritability of the muscle (as in chronaxie studies), or in investigating the electrical activity of resting muscles or of some groups of fibers within an actively contracting muscle. Electromyographic techniques can also be applied to the study of the muscle in relation to the nervous system, and the patterns of organization of muscle function within the framework of an investigation of the function of the nervous system can be studied. These latter have been confined in large measure to experimental studies in animals, and only quite recently have they been applied to humans for the study of the effects of disease, as well as an investigation of normal function (1-5). Thus, as electroencephalography is the clinical physiologic study of the highest level in the nervous system, so electromyography becomes a similar approach at the lowest level in the Jacksonian sense. In this regard it should be borne in mind that muscular activity is the end-product of the activity of the nervous system.

METHODS

Both electrical and mechanical responses to stimulation can be evaluated with the production of much useful information. Basic electronic apparatus which is

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necessary consists of a suitable preamplifier capable of magnifying without distortion electrical activity with frequencies as low as a tenth of a cycle per second and as high as five or eight thousand cycles per second, an amplifier and an oscillograph which can display the potentials for direct observation or permanent recording. This latter is most usefully an oscilloscope and camera arrangement. For stimulation the apparatus should allow variation of the intensity of the stimulus, its duration, how frequently it recurs, and the relationship of a second or of a group of stimuli to it. A number of techniques are available for recording mechanical activity. It is most convenient that the mechanical responses be converted into changes in electrical potential so that their time course in relation to the time course of the action potential can be evaluated. These devices, force transducers, are arranged and calibrated so that mechanical deformation of small degree causes a measurable change in potential.

The activity of small groups of muscle fibers of the resting muscle is studied by the insertion of electrodes within the depths of the muscle. The electrodes may be a single sharp needle insulated along its course except for a small bare area at its tip, or hollow needles containing an insulated single or double electrode. The patterns of electrical activity observed during the course of muscle activity vary somewhat depending upon type of electrode used (6); the choice of electrode is determined in part by the individual experience and interest of the electromyographer and in part by technical considerations such as the amount of ambient unwanted electrical noise. Utilization of the technique of electrode insertion into the depths of the muscle is the more common form of electromyographic study that is done (7-9). The information it provides may be of assistance in determining the presence of denervation, of increased irritability, or of local disease within the muscle.

Studies of the response to stimulation are accomplished by placing on the belly of the muscle an active electrode, usually a silver or stainless steel disc of several millimeters diameter, slightly cup-shaped, and on the tendon of the muscle an indifferent electrode. These electrodes detect a summation of the electrical activity in the local area of their placement and if suitably applied, with proper experimental design, changes in electrical activity which occur in their vicinity can be demonstrated to be the result of activity of the specific muscle or group of muscles under study. Surface electrodes do not provide, directly, evidence of denervation, nor can the electromyographer determine in the course of voluntary activity sufficient variation in the response of abnormal muscle as compared to healthy muscle to enable him to make a clear cut diagnostic statement as to the presence of disease.

Surface electrodes do, however, have a great utility in the study of the responses to stimulation of the nervous system. These studies one might call clinical electro-neurophysiology. The nerve-muscle preparation to be studied is selected by an evaluation of the clinical status and an interest in the type of electrical activity to be investigated. For example, it is convenient to study the electrical response to stimulation of the ulnar nerve by the activity of the abductor of the fifth finger or the activity of the first dorsal interosseus muscles.

One might also study the flexor carpi ulnaris. Nerves which can be investigated or stimulated are those which have along their course one or more points at which there are few or no intervening structures between them and the surface of the skin. Many of the peripheral motor nerves fit in this category. The entire brachial plexus, the axilla, the elbow and the wrist are loci for stimulating nerves coursing down the arm where there are few structures intervening between them and the electrodes. For nerves in the lower extremity the popliteal fossa, the head of the fibula, and the ankle are similarly available for studying the popliteal and peroneal nerves. When nerves are to be stimulated the patient is placed in a comfortable position and the surface electrodes are applied over the muscle to be recorded from. A suitable flat ground electrode is applied and the point of stimulation of the nerve selected. Two electrode discs are firmly applied to the skin overlying the nerve. The stimulus is perceived by the patient as a local shock, which is more surprising than annoying, and with good stimulating electrode placement the thresholds for eliciting the responses are low enough so that painful cutaneous stimulation does not occur. In order that movement artefact and changes in the response of the muscle due to changes in its length be minimized, if these are not the subject of investigation, isometric contraction of the muscle is obtained by fixation of its attachment using appropriate measures. One can study, of course, isotonic contraction with other mechanical arrangements.

Four areas of investigation have to date shown themselves to be productive. These are (a) a determination of the velocity of conduction of the nerve, (b) the alteration in the response to stimulation by pre-existing stimulus conditions, the use of drugs and other measures, (c) a study of the time and electrical course of events of reflex responses to stimulation of afferent peripheral nerves, and (d) the effect of exercise or tetanics on the electrical and mechanical response.

(a) Conduction Velocity

Helmoltz was the first to study accurately the velocity of conduction along the nerve. His method is the method in use today, with modification of the apparatus to use the more convenient electronic equipment now available. The transmission of the nerve impulse along a nerve takes a finite period of time which can be measured. Helmholtz' method consists of determining the latency of the response to stimulation of some point along the nerve at a distance from the effector and of the latency of the response at some point close to the effector and dividing the difference by the distance between them. Helmholtz did this by stimulating the nerve and recording its mechanical response. With the current electromyographic technique the electrical response in the effector is determined (1, 2, 10, 11). The time course can be exceedingly accurately measured and the duration and intensity of the stimulus well controlled. The determination of the latency of the response from one point along the nerve to the effector is insufficient to make a determination of conduction velocity as relatively the latency is greater in proportion to the distance very close to the muscle than it is farther from it. If a plot of the latency of the response against the distance from the

active electrode over the muscle is made (Figure 1) and the line connecting the points be extended through the abscissa or the point of zero distance, it can be observed that the curve does not pass through zero time but that a residuum of time remains. This residual latency, it is postulated, is a reflection of the processes of transmission of the nerve impulse at the myoneural junction and through the fine terminal arborization of the motor nerve. However, the latency of the response appears to have a direct relationship to the distance as one gets slightly farther from the muscle. This relationship is the velocity of the conduction of the nerve (Table 1).

Figure 2 demonstrates the characteristics of the response to stimulation of a normal ulnar nerve recorded from the hypothenar muscle group. The difference in the latencies is readily apparent. It will be noted that the amplitudes of the response from the two points stimulated, the elbow and the wrist, are equal. Under certain conditions of disease, particularly in the neuronitides, the latency of the response to stimulation at the distal point is much prolonged and the response has a marked decrease in amplitude and change in its configuration.

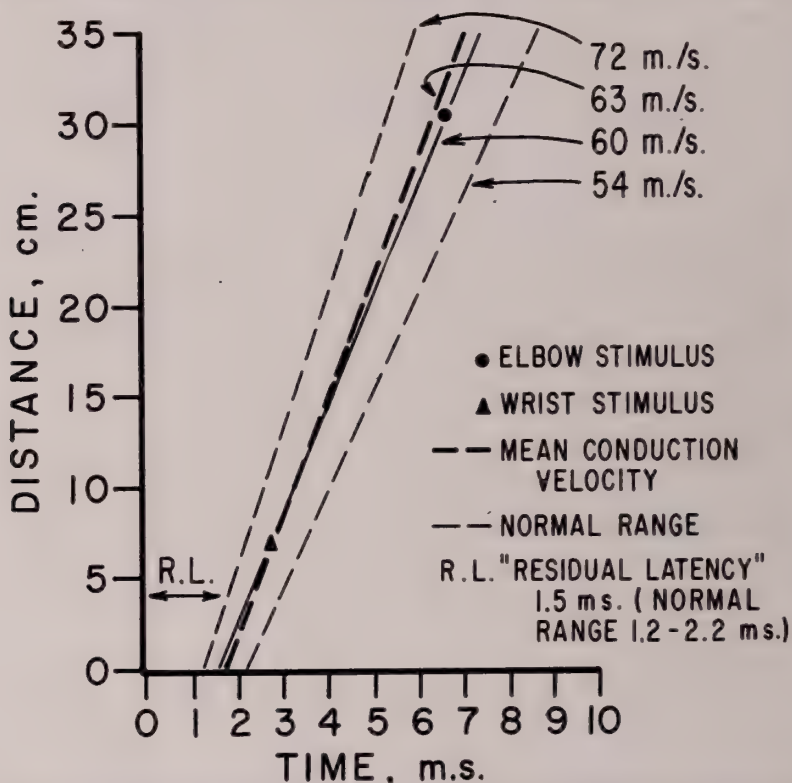


FIG. 1. Latency of the response plotted as a function of the distance between stimulus and muscle. The points are taken from the data of Case 6, Table 1. The slope of the line connecting the points is the conduction velocity. Normal limits (99% level of confidence) and the mean value are shown as the dashed lines. Note that if the curve is extended to the abscissa (0 distance) it does not pass through the origin. The shift to the right represents the residual latency (see text).

TABLE 1

Case	D ₁	D ₂	D ₁ - D ₂	t ₁	t ₂	t ₁ - t ₂	CV	RL
1	32.0	10.0	22.0	7.1	3.1	4.0	55	1.3
2	30.8	7.0	23.8	7.2	3.0	4.2	54	1.8
3	32.9	8.0	24.9	7.7	3.1	4.3	58	1.8
4	19.7	7.3	12.4	4.2	2.5	1.7	73	1.5
5	24.2	7.2	17.0	5.9	3.7	2.2	77	2.8
6	30.5	7.0	23.5	6.6	2.7	3.9	60	1.5
7	32.6	11.5	21.1	6.1	3.0	3.1	68	1.3
8	19.7	7.3	12.4	4.2	2.5	1.7	73	1.5
9	28.5	8.0	20.5	6.9	3.3	3.6	57	1.9
10	32.5	8.5	24.0	8.2	3.4	4.8	50	1.7
Mean							63	1.7
s.e. =							2.9	0.14
99% range =							±9	±0.5

Raw data from ten normal subjects for the calculation of conduction velocity and residual latency (illustrated in Figure 1 by case 6). D₁ is the distance in centimeters from the stimulating electrode at the elbow to the recording electrode; D₂ is the distance at the wrist. t₁ is the latency in milliseconds of the response at the elbow; t₂ at the wrist. CV is the calculated conduction velocity in meters second. RL is the residual latency in milliseconds.

The conduction velocity can be seen to be (D₁ - D₂)/(t₁ - t₂). Ranges expressed in regard to the mean are at the 99% confidence level using Fisher's t tables. (For further details see text.)

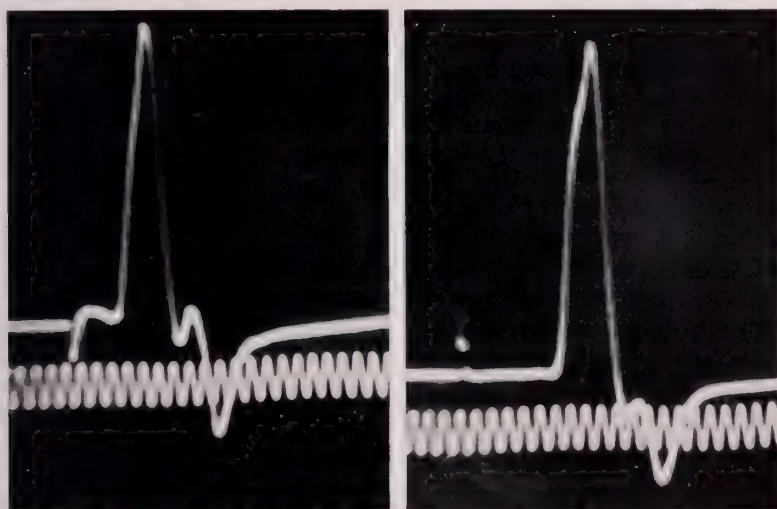


FIG. 2. Hypotenar muscle action potentials elicited on stimulation of the ulnar nerve at the elbow (right) and wrist (left) in Case 7, Table 1. Time is in milliseconds. The first upward (negative) deflection in each upper trace is the stimulus artefact, the second the action potential of the muscle which has contracted maximally as the result of the arrival of the volley of impulses which have travelled down the nerve from the point of stimulation. The difference in latencies between the more distant and closer point of stimulus application is evident.

When the nerve is stimulated close to the muscle the latency is almost normal and the amplitude of the response is much greater, almost normal. These observations suggest that the disease process is located proximally rather than distally in the nerve. Acute and prolonged ischemia causes changes in the velocity of conduction and cooling of the nerve and muscle causes the latency to be prolonged and the amplitude of response to alter (11). Physiologic investigations of the isolated mammalian nerve have disclosed velocities on the order of one hundred meters per second; in man with this technique they are sixty meters per second (1, 4, 10). This discrepancy is unexplained by changes in the technique and differences in the mode of measurement. Only a limited number of disease states have been studied in this fashion and the results are only beginning to be published. It can be seen that this technique offers a method for investigating the locus and nature of the pathologic physiology in a number of disorders of obscure type, called peripheral neuropathy or neuritis, associated with other diseases.

(b) The Excitability Cycle

The nature of the excitable process for transmission down the nerve and between the nerve and its effector has been an intriguing problem since the action of neurons has been under investigation. The excitability and responsiveness of nervous and muscular tissue alters according to the pre-existing conditions at the time of stimulation. Events which have occurred immediately preceding or at some distance preceding the stimulus have an effect upon the latency and amplitude of response. A previous tetany can cause a significant change in the characteristics and amplitudes of the response of a succeeding stimulus and this change alters as the time interval between the tetany and the stimulus changes. In addition a pre-existing conditioning single stimulus results in alterations in the latency and characteristics of the response to succeeding stimuli at varying time intervals. This latter type of study is called a study of the facilitation of the nerve-muscle preparation and offers a method for investigating some of the properties of this nerve-muscle preparation in health, and disease, and under various conditions of ambient temperature and drug administration (12-15). This appears to have some value in the study of the nature of the pathologic process which one sees in such alterations of function at the myoneural junction in myasthenia gravis, but is not confined to this disorder, for the function of the nerve and its muscle alter when the neurone is diseased as well. Characteristically after a supramaximal conditioning stimulus a succeeding test stimulus will evoke no response for a short period of time (approximately two milliseconds) and then a response of increasing amplitude to a level greater than the test response is able to achieve when given alone. This occurs in seven to eight milliseconds after the test stimulus; at about thirty milliseconds the test response is smaller than it was when given alone. This later process may go on from thirty to ninety or more milliseconds. Figure 3 shows a conditioning and test response series illustrating the facilitation and subsequent inhibition in the course of time. Changes in the mechanical response occur *pari passu* with these electrical changes and require further investigation (14).

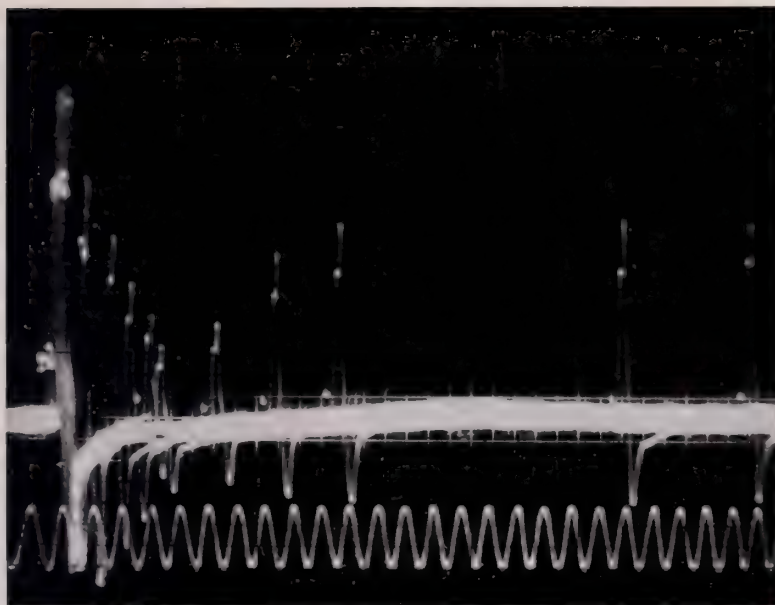


FIG. 3. Facilitation study. Using multiple oscilloscope sweeps the hypothenar response to a pair of stimuli applied to the ulnar nerve has been recorded. The interval between the stimuli has been varied so that the changes in the second (test) response are illustrated as a function of time (time trace 100 cps). The response at the left is that to a supramaximal conditioning stimulus. The initial facilitation (increase) of the test response, subsequent longer lasting inhibition and return to its control level are observed. (The test response is about 70% of maximal.) Pairs of stimuli were delivered at 5" intervals. Because of the time scale used here the absolutely and relatively refractory periods (usually up to $7\frac{1}{2}$ ms) cannot be seen.

(c) Reflex Responses in the Peripheral Nervous System

In 1922 Hoffman (16) described the occurrence of a response of prolonged latency when afferent nerves which innervated muscles showing stretch reflexes were stimulated. The latencies were in excess of what one would expect with the distances involved. These responses, called H reflexes, have definite electrical characteristics which make them easily identified (11). Wagman studied these extensively and showed that the latency is in part related to the size of the individual and established norms for the intervals between stimulus and response (17). These reflexes provide a method for studying the afferent portions of the nervous system and the proximal portions of the efferent system. Figure 4 shows the H reflex elicited from stimulation of the popliteal nerve and recorded from the triceps surae. When one investigates the excitatory process in this reflex the period of inhibition is noted to be very prolonged, running up to more than one second. This observation is in accord with studies of central synaptic relationships. Magladery and his coworkers investigated some of the properties of this reflex system in a series of experiments reported since 1950 (11, 18, 19). Aside from investigation of the time course and character of the response when there

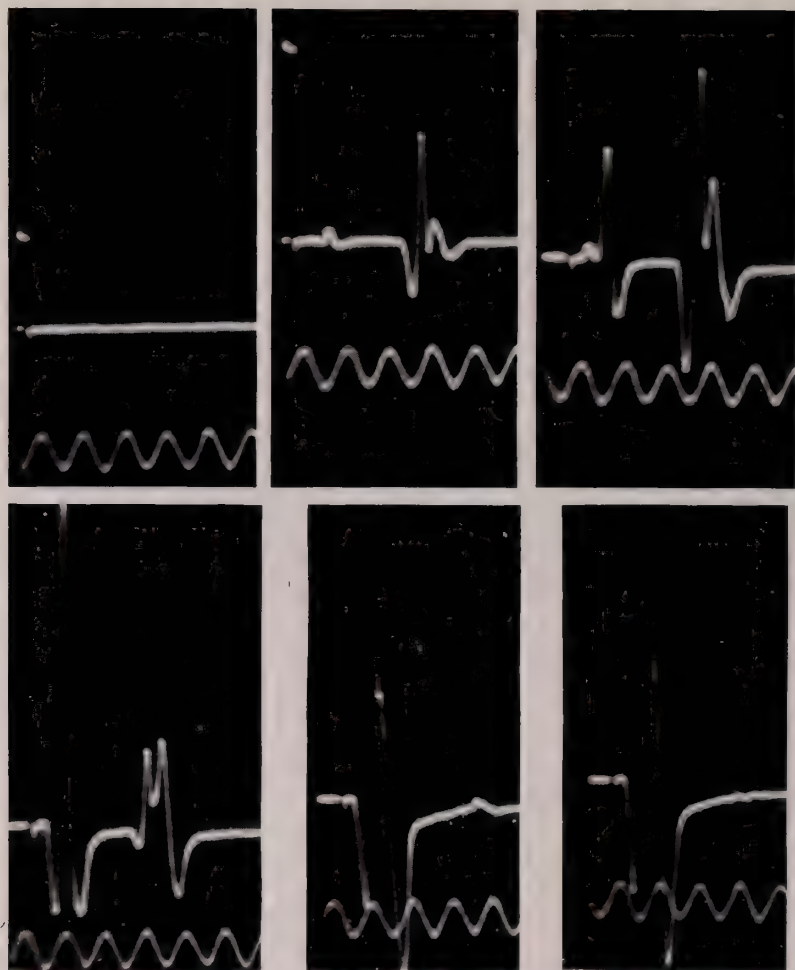


FIG. 4. The "*H* reflex": Stimuli of increasing intensity have been applied to the popliteal nerve and the action potential recorded from the calf muscle. (Lowest intensity in the left upper, highest in the right lower trace.) As the stimulus intensity increases there is a response of increasing amplitude after a prolonged latency. At higher levels of stimulus intensity the motor fibers are directly stimulated and an early response appears. Further increase in stimulus intensity eventually results in obliteration of the reflex response under these conditions. Magladery (18) demonstrated that an antidromic volley (one that travels up the motor nerve toward the spinal cord) renders the nerve refractory to the reflexly induced volley of stimuli and thus prevents the reflex impulses from reaching the muscle. (Time 100 cps.)

is cord transaction there is little information about these reflexes as they are influenced by tetanics and by disease processes. This group of phenomena will provide some indication as to the pathophysiology at lower levels in the central nervous system, and in the proximal portions of the nerves and roots in a number of diseases.

(d) The Effect of Previous Tetanics

Botelho and her co-workers have in recent years conducted investigations of the effect of a tetany (repetitive stimulus at moderate frequency up to fifty per second) on the post-tetanic electrical and mechanical response to a single stimulus (20-22). They have demonstrated that in the intact human under normal conditions a significant potentiation of the contraction occurs under these conditions. The time-course of these phenomena varies with alteration in ambient temperature, ischemia, drugs and in the presence of myasthenia gravis. These provocative studies, which are somewhat at variance in their conclusions with those of other workers (23) provide another clinical physiologic area for further investigation.

SUMMARY

A technique for the investigation of the electrical and mechanical responses to stimulation of human peripheral nerve has been described. Four areas of physiologic investigation in health and disease of the nervous system and its muscular effectors have been referred to as clinical electroneurophysiology using the electromyograph.

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Radiological Notes

CASE NO. 9

H. S., a 40 year old woman, was admitted with a chief complaint of weakness and clumsiness of her left leg and left arm. For 25 years, she complained of headaches attributed to sinusitis. Fourteen years prior to admission, the patient had a thyroidectomy, after which she gained 50 pounds. The reason for the thyroidectomy is not clear. Neurological examination demonstrated a left hemiparesis and left hypalgesia. Electroencephalogram showed a slow focus in the right upper posterior frontal region. Roentgen examination of the skull (Figs. 1a, 1b) showed marked thickening of the calvarium on the right side of the posterior frontal and

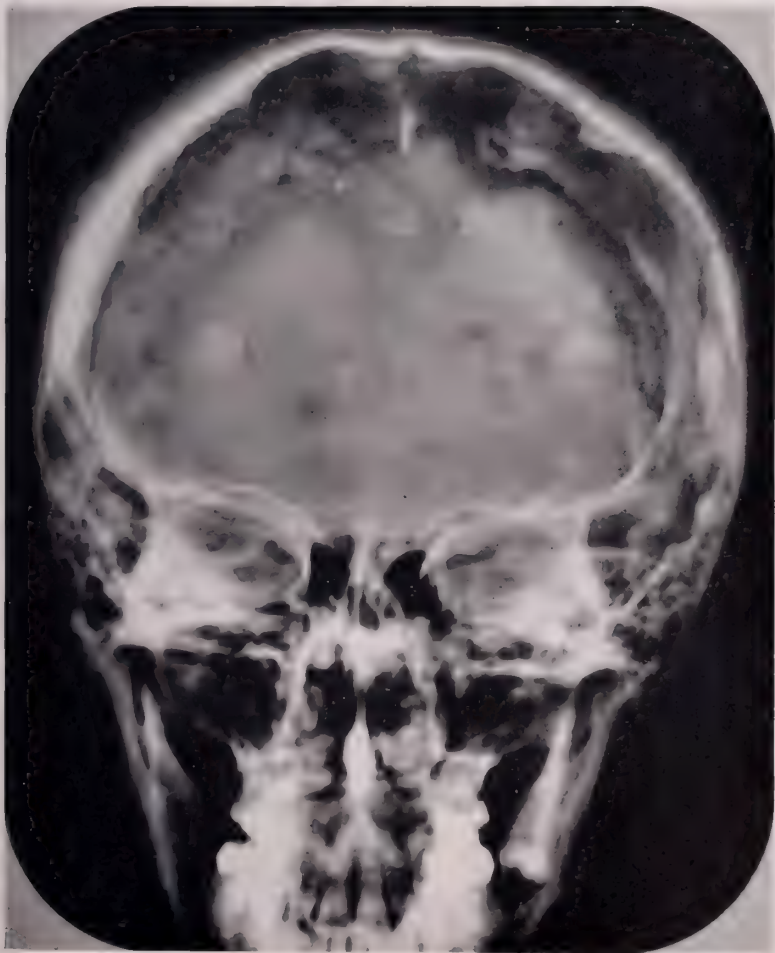


FIG. 1a. P. A. view of the skull shows marked diffuse thickening of the right side of the calvarium in the frontoparietal region. Numerous enostoses are present, particularly on the left side. Large diploic channels are present on both sides, somewhat more marked on the left.

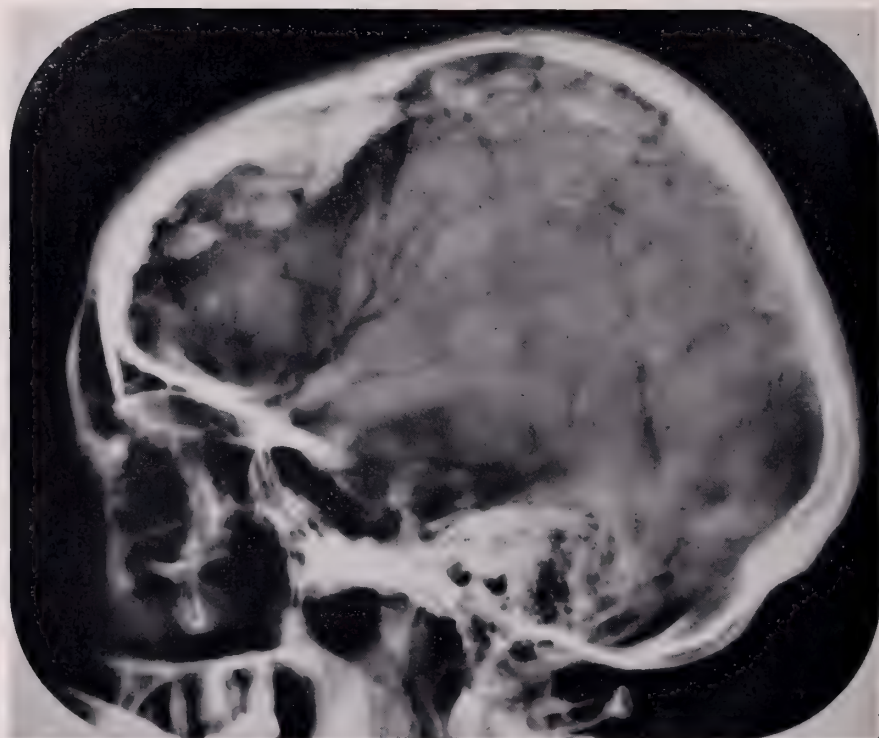


FIG. 1b. Lateral view of skull confirms widespread enostoses, especially in the left frontal bone. Several small, bony projections are scattered posteriorly as well. The dorsum and floor of the sella turcica are demineralized.

parietal regions with marked irregularity of the inner table; i.e., a diffuse hyperostosis. In addition, there were a large number of discrete and partially confluent enostoses on both sides of the skull, most marked in the left frontal region. In places, e.g., in the left anterior frontal region, the appearance was rather typical of hyperostosis frontalis interna. Vascular markings were prominent in all portions of the calvarium. The sella turcica was not enlarged but the posterior clinoids and the floor of the sella were demineralized.

Right carotid angiogram (Fig. 2) showed separation and elongation of the middle cerebral arterial branches in the posterior frontal and parietal regions. The anteriorly displaced ascending frontoparietal artery showed an arcuate course, convexity anteriorly. There was also an arcuate, course convexity posteriorly of a posterior ascending (marginal) branch of the pericallosal artery. A group of small tortuous vessels was present in the superior parietal area.

At craniotomy, a large frontoparietal flap was raised. The bone was unusually thick and the inner table irregular and adherent to the dura and to a bilobed meningeal tumor extending parasagittally. Each lobe was the size of a large walnut. This mass was removed. In addition, multiple scattered smaller meningeal tumors were noted in the exposed area, which were curetted. Another fairly

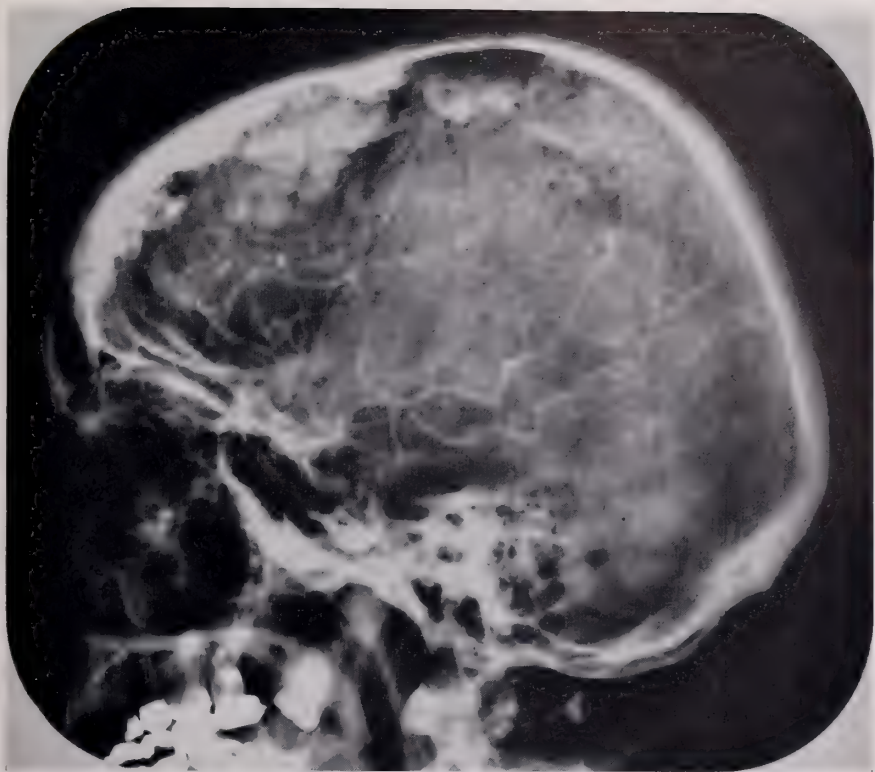


FIG. 2. *Right carotid angiogram lateral view*

large meningeoma en plaque adjacent to the longitudinal sinus was excised. Postoperatively, the patient showed marked improvement.

It was apparent that this patient was suffering from multiple meningiomata (meningiomatosis). A left sided angiogram (Fig. 3) was performed and demonstrated depression of the vessels in the posterior portion of the Sylvian fissure with separation and a vertical course to the ascending branches over the convexity. The findings were clearly abnormal but difficult to interpret on the basis of a single mass lesion.

It is of interest that in this patient a combination of hyperostosis frontalis interna and hyperostoses due to multiple meningiomata appeared to be present. Differentiation of individual enostoses clearly creates considerable difficulty.

Final diagnosis: Cerebral meningiomatosis.

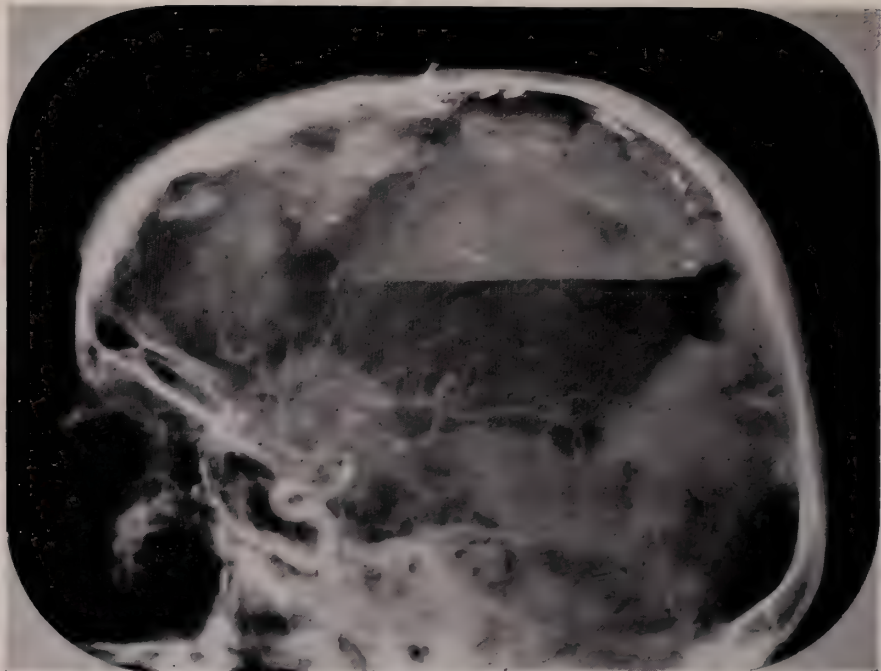


FIG. 3. *Left carotid angiogram lateral view.* This was done after craniotomy had been performed on the right side.

CASE NO. 10

First admission of a 75 year old woman with the chief complaint of abdominal pain for three weeks. Physical examination showed slight tenderness in the left upper quadrant, but no definite mass was palpable. Barium examination (Figs. 1a, 1b) showed a large, non-obstructive, irregular filling defect in the distal limb of the splenic flexure. This defect was sharply demarcated at both ends by a thick ring of tissue, while its central portion was irregularly excavated with large nodular masses lining its periphery. The appearance was clearly that of a malignant neoplasm. However, because of the increased rather than diminished calibre of the bowel lumen, it was considered that the most likely diagnosis was lymphosarcoma. At laparotomy, a large mass was found in the splenic flexure. This was resected and reported as a lymphosarcoma on microscopic examination.

Final diagnosis: Lymphosarcoma of the colon.

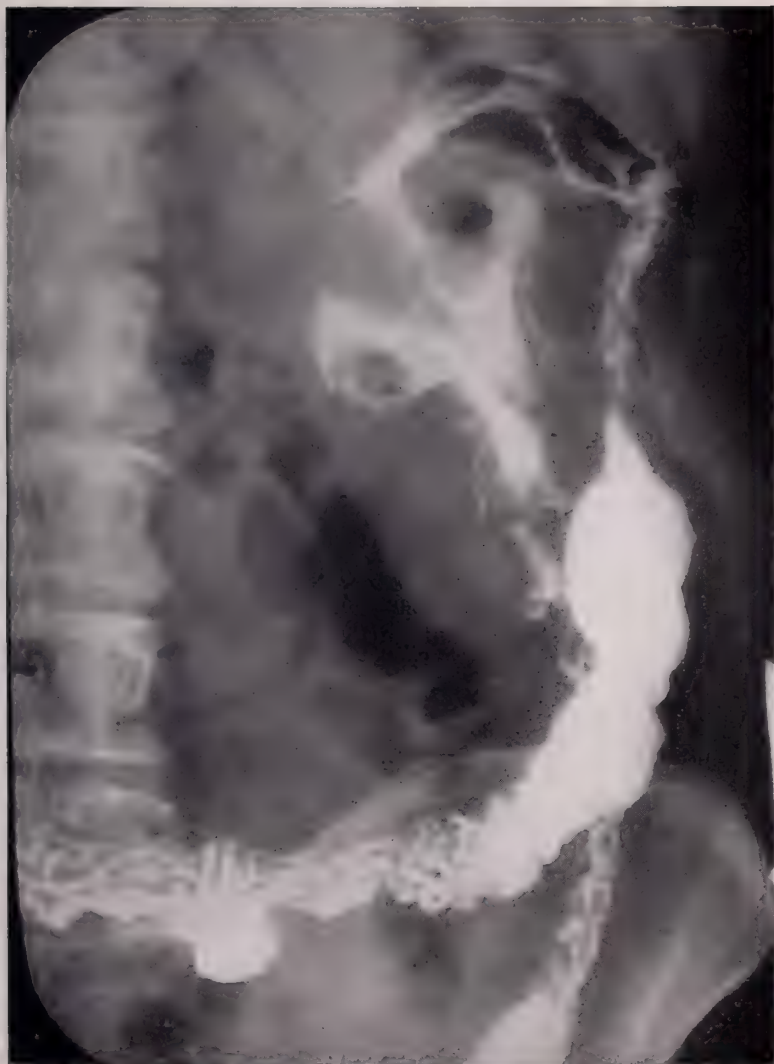


FIG. 1a. Barium enema film after evacuation shows a large, irregular, multinodular lesion in the distal limb of the splenic flexure. The mucosa is obviously destroyed; the lumen is not narrowed.

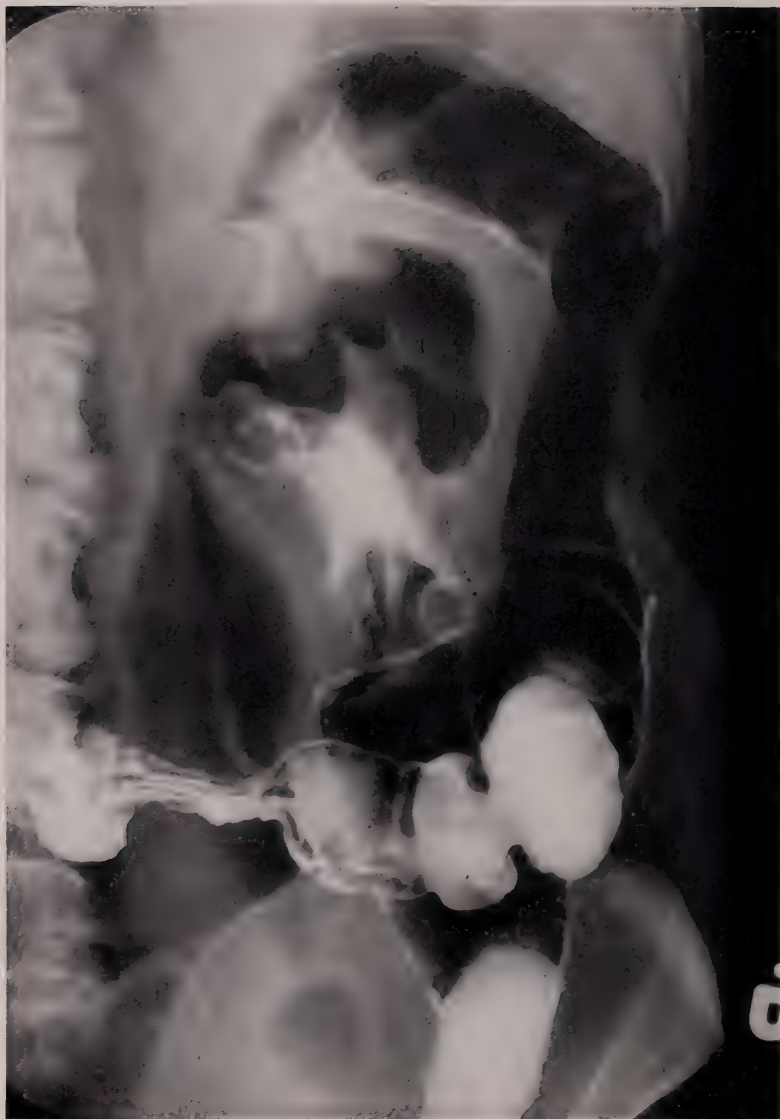


FIG. 1b. Double contrast view of the lesion shows that the calibre of the bowel lumen in the center of the lesion is increased. The grossly nodular defects project into the lumen. At each end, there is a thick "overhanging" edge.

CASE NO. 11

D. S., a 58 year old male, was admitted with the chief complaint of epigastric pain occasionally radiating to the mid-back for six months. The pain often occurred after meals and at night and was relieved by alkalis. Barium meal examination (Figs. 1a, b, c, d) showed an ovoid, sharply demarcated ulcer crater which appeared to be located in the antrum of the stomach. The impression was that of a benign gastric ulcer.

Laparotomy and subtotal gastrectomy were performed. A deep, punched out ulcer, 1.5 cm by 1.0 cm was found in the duodenum. The proximal margin of



FIG. 1a. Ovoid ulcer pocket apparently in the antrum associated with marked spasm

the ulcer was located about 0.5 cm distal to the pyloric ring. The ulcer was adherent to the pancreas and its base had to be taken off the pancreas by sharp dissection. The serosa over the duodenum was markedly thickened, scarred and edematous. The pyloric ring was markedly hypertrophied.

This case demonstrates the difficulty which may exist in distinguishing a duodenal from a gastric ulcer in the presence of marked spasm and deformity. A callous ulcer of this type in the duodenum is unusual.

Final diagnosis: Callous penetrating duodenal ulcer masquerading as a gastric ulcer.



FIG. 1b. Somewhat better filling shows the presence of thick folds beyond the crater apparently in the base of the bulb.

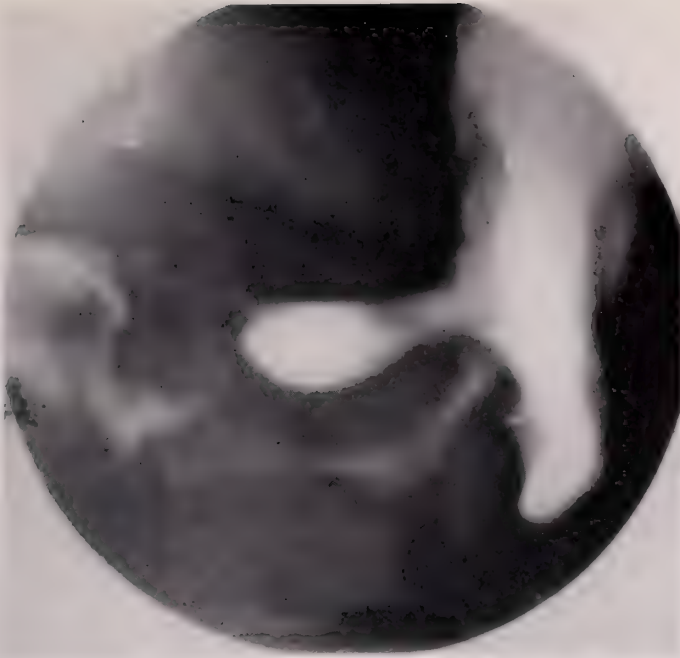


FIG. 1c. Erect spot film shows thick folds below and parallel to the crater at a considerable distance from it. Persistent narrowing proximal to the crater.



FIG. 1d. Erect spot film shows that the narrowed channel proximal to the crater joins the vertical portion of the stomach along its lesser curvature.

CASE NO. 12

M. H., a 46 year old woman, had numerous complaints which included a "nervous stomach." For several years, she complained of right lower quadrant and lower abdominal colicky pains, which had increased in severity during the previous month. Physical examination was non-contributory. Hemoglobin was 12.9 gms., stools were guaiac positive on two occasions. Rehfuess test showed free acid up to 10 units. Barium meal examination (Fig. 1a) showed a smooth, globu-



FIG. 1a. Smooth globular defect almost completely filling the duodenal bulb

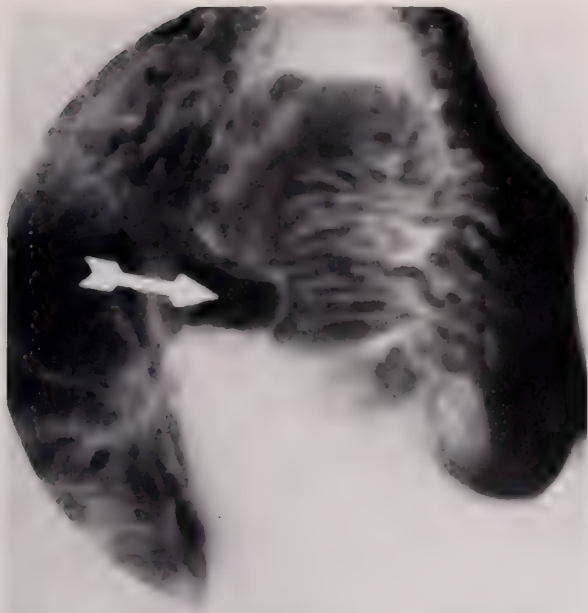


FIG. 1b. Spot view shows the thick pedicle occupying the pyloric canal

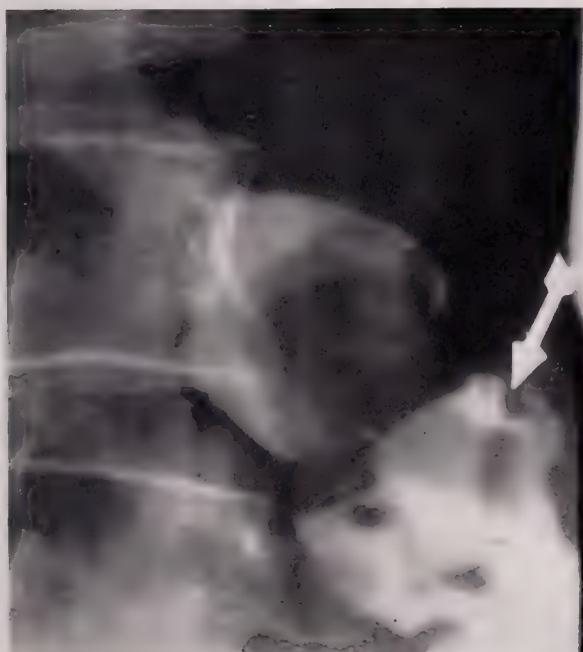


FIG. 1c. Polygraph view shows that pedicle is attached to the lesser curvature of the antrum of the stomach about 1 cm. proximal to the pylorus.

lar filling defect about 2 cm. in diameter within the duodenal bulb. Spot and polygraph views (Figs. 1b, 1c) demonstrated a stalk traversing the pylorus and connecting the defect to the lesser curvature of the antrum of the stomach. There was no evidence of any obstruction to the passage of barium and no retained secretions in the stomach. This patient refused operation.

Final diagnosis: Gastric polyp on a pedicle prolapsing into the duodenal bulb.

CASE NO. 13

E. A., a 79 year old male, was admitted with a history of tarry stools of two months, increasing weakness and weight loss. Hemoglobin had fallen to 22 per cent. Four transfusions had been given. Upon admission, hemoglobin was 9.6 gms. and stools were 4 plus guaiac. On Rehfuess test, no free acid was present and combined acid did not exceed 8 units. Barium examination showed a bizarre changing deformity of the gastroduodenal region (Figs. 1a, b, c, d).



FIG. 1a. Wedge shaped filling defect in the duodenal bulb with transverse folds at the base. Two peculiar collections of barium distal to the defect.

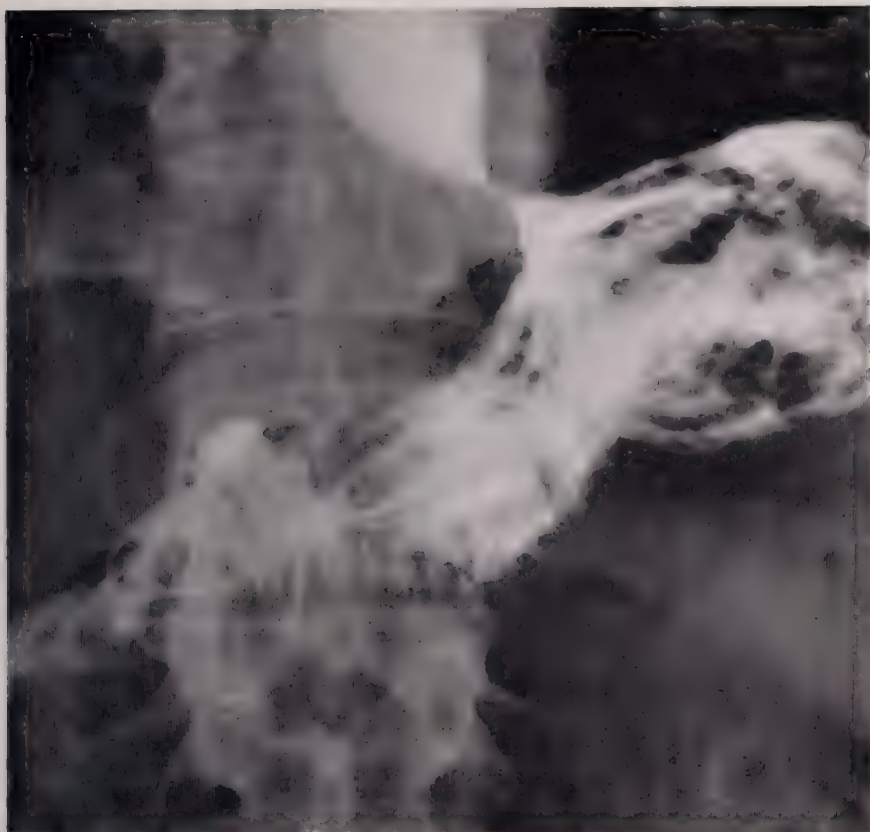


FIG. 1b. Transverse folds at base of bulb more numerous. A central streak of barium appears to extend into the proximal portion of the defect from the stomach.

After transfusions, the patient was explored and a mass the size of a golf ball was felt in the first portion of the duodenum. This was easily milked up and replaced into the stomach. After resection, it was evident that the mass consisted of two polypoid projections arising from a common base 2 cms. in diameter on the lesser curvature of the stomach, located 5 cms. proximal to the pylorus. Microscopic examination was reported as two benign pedunculated adenomata.

Final diagnosis: Benign gastric polyps with gastroduodenal intussusception.



FIG. 1c. Multiple irregular collections of barium in gastroduodenal region



FIG. 1d. An apparent quadrangular defect in the antrum; the bulb has a comma configuration.

CASE NO. 14

F. R., a 77 year old male, was admitted with the complaint of epigastric pain and loss of 30 pounds in weight over a period of six months. On physical examination, an epigastric mass was palpable. The hemoglobin was 6.4 gms., stools were guaiac positive, total acid was 88 and free acid 64 units on Rehfuss test. Barium meal examination (Figs. 1a, 1b) showed a large irregular multilobular defect filling the antrum and duodenal bulb. The portion in the bulb was completely surrounded by barium, except at the pyloric ring.

Subtotal gastric resection was done. A large polypoid ulcerated carcinoma 8 cms. long occupied the distal part of the stomach. A portion of the distal margin of the tumor had apparently prolapsed into the duodenal bulb. The duodenal mucosa was congested but intact, and grossly, the tumor stopped at the pyloric



FIG. 1a. Irregular multilobular filling defect in the antrum and bulb. The periphery of the bulb appears complete except at its base.

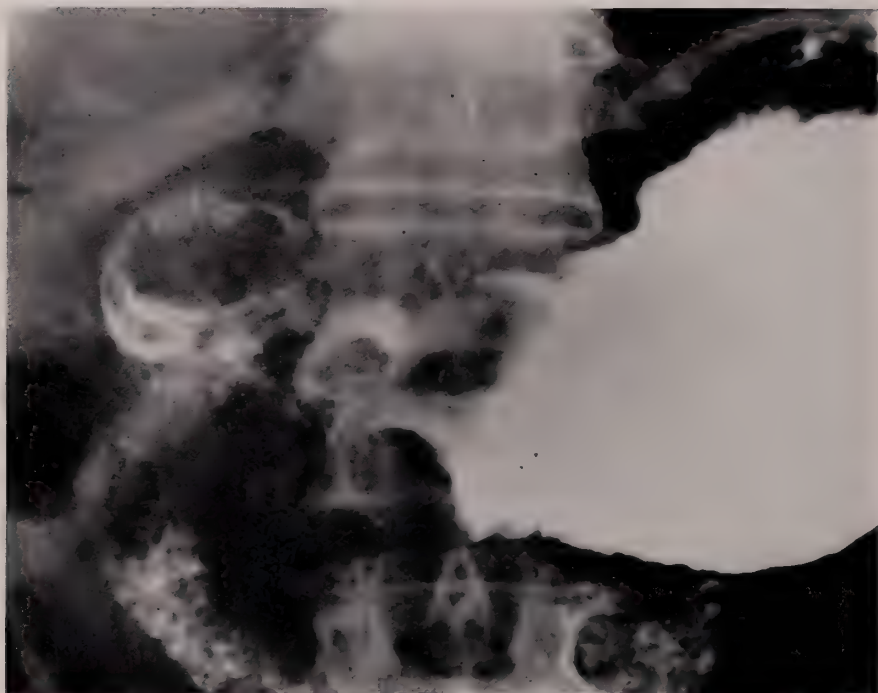


FIG. 1b. Multilobular character of the tumor mass in the antrum and bulb again evident

ring. Microscopically however, submucosal extension into the duodenum was seen.

Final diagnosis: Polypoid carcinoma of the stomach with partial prolapse into the duodenal bulb.

CASE NO. 15

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C. S., a 46 year old housewife, was admitted with the chief complaint of epigastric pain and nausea for six months and vomiting for one month. The epigastric pain was steady and boring in nature, somewhat relieved by food. Pain



FIG. 1a. Shows complete destruction of the mucosal pattern of the antrum with rigid scalloped contours. Proximal margin is sharply demarcated.

at night was severe and relieved by milk. There was no history of hematemesis or tarry stools. Clinical diagnosis was duodenal ulcer. Barium meal examination (Figs. 1a, 1b) however, showed a large, rigid, ulcerated area involving the entire antrum of the stomach, extending into the base of the bulb. The antrum was slightly narrowed with scalloped contours, but the base of the bulb was unusually wide. The margin of the tumor in the bulb was sharply demarcated. A pyloric channel could not be visualized. The diagnosis of lymphosarcoma of the stomach was made primarily on the basis of the widened, infiltrated duodenal bulb. This was confirmed by gastric resection, which demonstrated that the neoplasm did involve the bulb. The microscopic report was lymphosarcoma.

Final diagnosis: Lymphosarcoma of the stomach extending into the duodenal bulb.

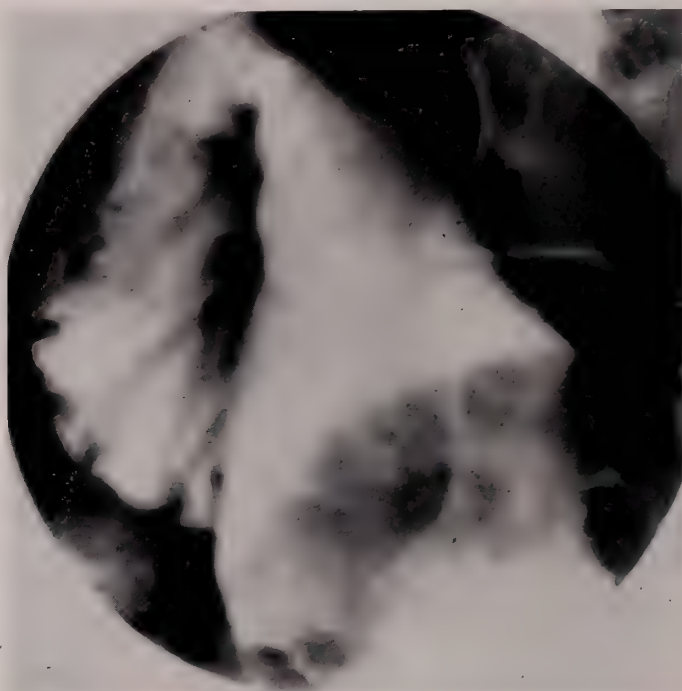


FIG. 1b. Spot film with light compression shows distal margin to occupy and widen the base of the bulb.

CASE NO. 16

S. S., a white male of 66 years, was admitted for investigation of an asymptomatic mass known to be present on chest films for a period of about nine years. History was not contributory. Roentgen examination of the chest (Figs. 1a, 1b) showed a homogeneous, sharply demarcated density about three inches in diameter near the base of the right lung field. In the left oblique view, the mass appeared somewhat hemispherical in shape, with its widest diameter on the lateral chest wall. No abnormality was noted in the adjacent ribs. On fluoroscopy, with the patient erect, the mass appeared to be fixed despite respiration. However, with the patient supine, the range of motion of the diaphragm was considerably greater and it was evident that the mass moved synchronously and in the same direction as the diaphragm. The appearance of the mass suggested that it was pleural in location and synchronous motion of the diaphragm indicated that the mass was in, or attached to, the lung. It was therefore concluded that

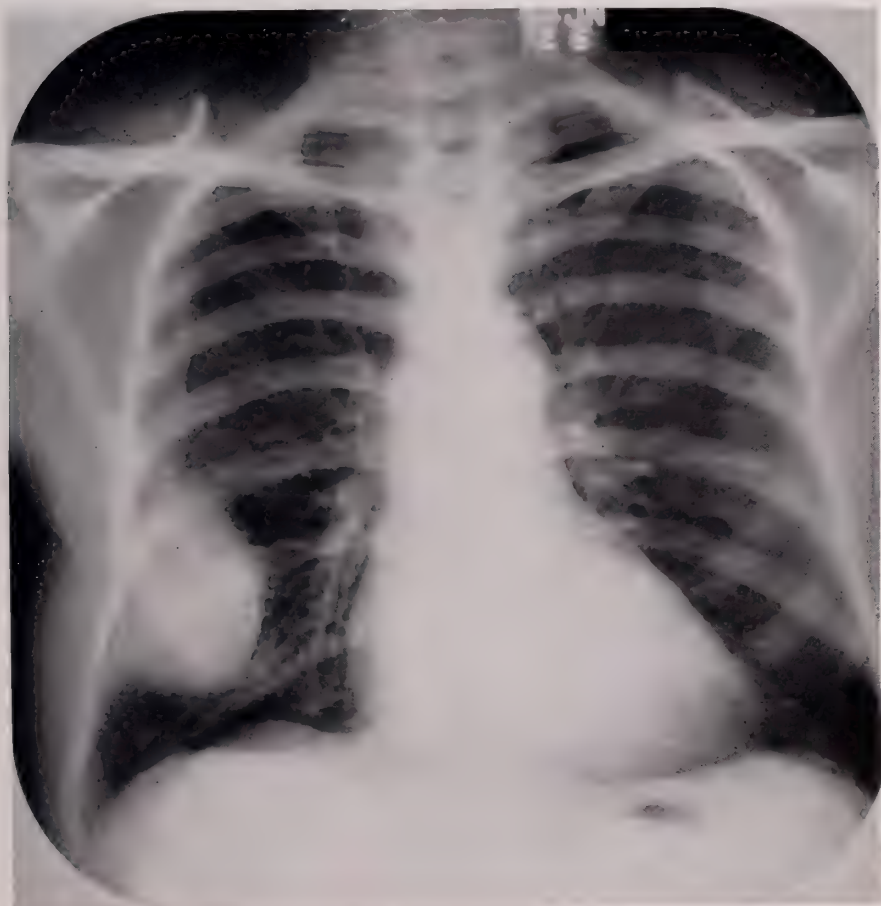


FIG. 1a. P. A. film of the chest wall shows a well demarcated homogeneous density a short distance above the diaphragm.

a benign tumor, presumably a fibroma, was present in the visceral pleura. For confirmation of the diagnosis, since the patient refused operative intervention, a small pneumothorax was induced. This demonstrated that the mass was attached to the right upper lobe by a short pedicle (Figs. 2a, 2b). When the patient was placed in the Trendelenburg position, the mass moved freely into the apex of the pleural cavity (Fig. 3).

Three weeks after the pneumothorax, the patient was readmitted because of right chest pain and fever. Roentgen examination showed the presence of a pleural effusion of moderate size and pleural tap showed it to be sanguinous. Thoracotomy was performed and a fibroma on a short pedicle resected. The



FIG. 1b. Left anterior oblique view of the chest confirms the very sharp demarcation of the density from the lung and its broad base on the lateral chest wall.



FIG. 2a. Induced pneumothorax, the patient erect, shows the mass near the bottom of the pleural cavity completely surrounded by air, except for a short pedicle (arrow) attaching it to the right upper lobe.

pedicle had twisted and the tumor was partially infarcted. It was assumed that the twisting of the pedicle was related to the excessive mobility of the mass in the presence of the pneumothorax.

Final diagnosis: Fibroma of the visceral pleura.

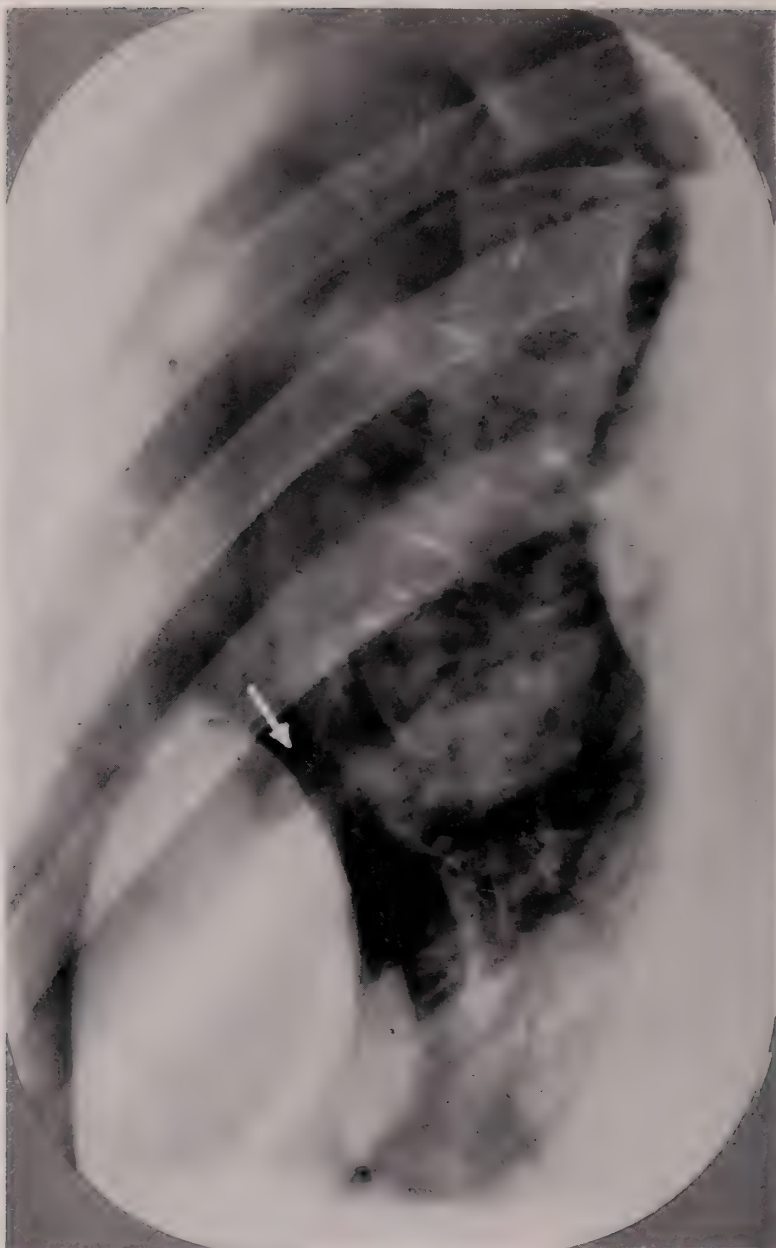


FIG. 2b. Same as Fig. 2a. (Arrow indicates the pedicle)



FIG. 3. Induced pneumothorax, with the patient in Trendelenburg position, shows that the mass has fallen into the apex of the pleural cavity.

CASE NO. 17

A 45 year old male was admitted because of a mass known to be present on chest films for at least five, and possible ten years. Patient had no complaints. Roentgen examination of chest showed in the P. A. projection (Fig. 1a) a very faint, poorly demarcated density about $2\frac{1}{2}$ inches in diameter at the level of the ninth intercostal space posteriorly. In the lateral projection (Fig. 1b), the shadow was hemispherical with its base directed posteriorly on the thoracic cage. Anteriorly, the lesion was very sharply defined and demarcated from the lung by a sharp, thin line, beneath which a lucent band could be seen over the surface of the mass. The appearance suggested a benign tumor of the chest wall extending into the pleural cavity and elevating the parietal pleura. At thoracotomy, the pleural cavity was entered and was free of adhesions; the parietal pleura



FIG. 1a. P. A. chest film showing faint, poorly demarcated density near the right base



FIG. 1b. Lateral projection demonstrates that the mass is hemispherical in nature and sharply demarcated from the lung by a thin line, deep to which a lucent band can be seen covering the tumor mass.

was bulged locally by a subpleura lipoma, which appeared to extend into the intercostal space. The tumor was removed without incidence.

Final diagnosis: Lipoma of the parietal pleura, or, subpleura lipoma of the chest wall.

CASE No. 9 CEREBRAL MENINGIOMATOSIS

CASE No. 10 LYMPHOSARCOMA OF THE COLON

- CASE No. 11 CALLOUS PENETRATING DUODENAL ULCER MAS-
QUERADING AS A GASTRIC ULCER
- CASE No. 12 GASTRIC POLYP PROLAPSING INTO THE DUO-
DENAL BULB
- CASE No. 13 GASTRIC POLYP WITH GASTRODUODENAL INTUS-
SUSCEPTION
- CASE No. 14 POLYPOID CARCINOMA OF THE STOMACH WITH
PARTIAL PROLAPSE INTO DUODENAL BULB
- CASE No. 15 LYMPHOSARCOMA OF STOMACH EXTENDING INTO
DUODENAL BULB
- CASE No. 16 FIBROMA OF THE VISCERAL PLEURA
- CASE No. 17 LIPOMA OF THE PARIETAL PLEURA, OR, SUB-
PLEURA LIPOMA OF THE CHEST WALL

THE JOSEPH H. GLOBUS MEMORIAL PRIZE

The third annual award of the Joseph H. Globus Memorial Prize has been presented to Dr. Ezra M. Greenspan for his paper entitled, "Clinical Survey of Globulin Distribution Patterns Determined by Simple In Vitro Laboratory Methods" which appeared in the March-April issue of *The Journal of The Mount Sinai Hospital*, Volume xxiii. The prize committee consisted of Dr. Paul Klemperer, Chairman, Dr. Eli Moschoewitz and Dr. John H. Garlock. The prize is offered only "to members of the staff up to the level of assistant attending in order to stimulate interest in the *Journal of The Mount Sinai Hospital*."

The award is named for Dr. Joseph H. Globus, who founded and for many years zealously served as editor of the *Journal of The Mount Sinai Hospital*.

THE DR. RALPH COLP AWARD

The colleagues, friends and patients of Dr. Ralph Colp have established at The Mount Sinai Hospital a fund to be known as the Dr. Ralph Colp Fund. From its income an annual prize, the Dr. Ralph Colp Award, will be given to a member of the House Staff for the best paper published in the Journal of The Mount Sinai Hospital. Preference will be given to a report dealing with a surgical subject. Dr. Ralph Colp has always had a fostering interest in the development of young physicians and the Fund committee felt that this was an appropriate way of honoring him.

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THE JOURNAL OF
THE MOUNT SINAI HOSPITAL

SYMPOSIUM
ON THE
MALABSORPTION
SYNDROME

David Adlersberg, M.D.

Guest Editor

INTRODUCTION

A classical description of the clinical entity presented in this symposium, the malabsorption syndrome, reads as follows:

"Wherefore they have flatulence of the stomach, continued eructations, or a bad smell; but if these pass downwards, the bowels rumble, evacuations are flatulent, thick, fluid or clayey, along with the phantasy, as if a fluid were passing through them; heavy pain of the stomach now and then, as if from a puncture; the patient emaciated and atrophied, pale, feeble, incapable of performing any of his accustomed works. But if he attempts to walk, the limbs fail; the veins in the temples are prominent, for owing to wasting, the temples are hollow; but also over all the body the veins are enlarged, for not only does the disease not digest properly, but it does not even distribute that portion in which the digestion had commenced for the support of the body; it appears to me, therefore, to be an affection, not only of the digestion, but also of the distribution."

Aretaeus the Cappadocian (second century A.D.) is credited with the above earliest description of this disorder (1). Hanes believes that "although it is admittedly difficult to identify ancient description with modern disease entities, yet one familiar with the sprue syndrome will hardly fail to recognize the lineaments of sprue in Aretaeus's graphic portrayal" (2). Paraphrasing Aretaeus' last sentence we like to consider him a precursor of those who believe that the malabsorption syndrome is an affection "not only of the digestion but also of the metabolism."

After an interval of many centuries Samuel Gee presented towards the end of the 19th century his studies "On the Coeliac Affection" (3).

"There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children between one and five years old. Signs of the disease are yielded by the faeces, being loose, not formed, but not watery; more bulky than the food eaten would seem to account for; pale in colour as if devoid of bile; yeasty, frothy, an appearance due to fermentation; stinking, stench, often very great, the food having undergone putrefaction rather than concoction. . . ."

"The causes of the disease are obscure. Children who suffer from it are not all weak in constitution. Errors in diet may perhaps be a cause, but what errors. . . ."

"Naked-eye examination of dead bodies throws no light upon the nature of the coeliac affection; nothing unnatural can be seen in the stomach, intestines, or other digestive organs. . . ."

"The patient wastes more in the limbs than in the face, which often remains plump until death is nigh. In the limbs emaciation is at first more apparent to hand than to eye, the flesh feeling soft and flabby. . . . the belly is mostly soft, doughy, and inelastic; sometimes distended and rather tight. Wind may be troublesome and very foetid. Appetite for food differs in different cases, being good, or ravenous, or bad. . . ."

"When recovery is incomplete, the illness drags on for years; the patient getting better on the whole, but being very subject to relapses of his complaint. While the disease is active the children cease to grow; even when it tends slowly to recovery, they are left frail and stunted. . . ."

This contribution of Samuel Gee is considered "a classic, and very little has been added to Gee's clinical and pathologic observations by subsequent writers"

(2). It is of interest that in Gee's opinion children and adults were similarly affected. Gee was probably the first author to express, as early as 1888, the view that celiac disease in children is analogous to sprue in adults.

During this century and especially in the last two decades there has been increasing interest in the clinical manifestations as well as in laboratory and autopsy findings in the malabsorption syndrome. Important information has been contributed in various parts of the world, especially in Britain, Scandinavia, the United States and other American countries, as may be seen from the extensive references appended to the subsequent articles of the symposium. Increasing evidence supports the concept that tropical sprue, non-tropical sprue, often referred to as the idiopathic steatorrhea syndrome, and celiac disease of childhood, are clinical varieties of the same metabolic disorder, primary or idiopathic malabsorption syndrome. Nevertheless some authorities in the field (4) are of the opinion that these conditions are "outwardly similar but inwardly dissimilar". A critical analysis reveals however that these dissimilarities, interesting as they may be (5), are too superficial to warrant definition of tropical and non-tropical sprue and of celiac disease as independent clinical entities. Celiac disease as seen today appears to be a milder variety of the malabsorption syndrome occurring in children. None of the clinical features are limited to this form of the malabsorption syndrome. The complications of celiac disease such as retardation of growth and rickets are fully explained by the onset of the symptoms of the disorder in childhood. On the other hand similar complications may be seen in adults with sprue, such as osteomalacia with various degrees of bone changes (6). The response of celiac disease to gluten-free diets again is not specific since adults with malabsorption syndrome, especially the milder forms, also may respond satisfactorily.

Although "cure" was more frequently observed in celiac disease and in the tropical variety of sprue than in non-tropical sprue, recent extensive studies revealed persistence of the metabolic abnormality and radiologic small bowel signs in seemingly asymptomatic celiacs (7) and in patients with "cured" tropical sprue (8).

The high familial incidence of celiac disease is well documented (9). Students of tropical sprue frequently report the occurrence of the disease in several members of the same family ("sprue houses") (10). In non-tropical sprue familial occurrence is no rarity according to our own observations and those of many others (10-12).

In the broader view of today primary malabsorption syndrome may be defined as a genetically transmitted metabolic disorder. Intestinal malabsorption and hematologic changes are the main facets of clinical interest. There are in addition many other metabolic abnormalities not necessarily related to the absorptive and hematic difficulties as will be demonstrated in some of the following papers. Profound disturbances in genetically controlled, enzymatic chain reactions apparently affect intestinal absorption as well as the metabolism of proteins, lipids, electrolytes and water. Despite the genetic anlage, the malabsorption syndrome may become manifest at various periods of life. In analogy

to other inherited errors of metabolism, e.g., diabetes, malabsorption syndrome may become clinically manifest in infancy or childhood as celiac disease, or later in life as tropical or non-tropical sprue. Actually a number of our patients with non-tropical sprue presented celiac disease in childhood. The stress of tropical climates, preceding tropical or non-tropical infections, malnutrition and probably wheat or rye gluten are important precipitating factors or triggering mechanisms. These factors will convert a predisposed person with "latent malabsorption syndrome" into a patient with "manifest malabsorption syndrome".

Primary malabsorption syndrome must be strictly separated from secondary malabsorption syndromes. In primary malabsorption syndrome there are no clinical roentgenologic or post-mortem evidences of gross organic disease entities involving the gastrointestinal tract, pancreas or liver. In secondary malabsorption syndromes gross pathologic alterations may be encountered in the gastrointestinal tract, such as extensive lymphosarcoma or amyloidosis of the small bowel and or the mesenteric lymph glands, intestinal lipodystrophy or certain forms of jejunoileitis; or after-effects of surgical procedures, such as extensive resection or exclusion of parts of the small bowel; or pathologic conditions in the pancreas, such as pancreatitis or carcinoma; or changes in the liver or biliary tree, such as mechanical biliary obstruction. Secondary malabsorption syndromes mimic the primary form but can be differentiated on clinical grounds, by the use of laboratory procedures and eventually by biopsy or autopsy.

The symposium presented in this volume is primarily concerned with primary or idiopathic malabsorption syndrome. The physiologic aspects of intestinal absorption are presented first. Abnormalities in the metabolism of proteins and lipids, of water and electrolytes are then discussed as well as disturbances in the intestinal uptake of vitamin B12 and in pancreatic enzymes. The subsequent papers deal with pathologic findings based on autopsy and biopsy studies. The presentation of the clinical aspects is based on analysis of a selected group of 94 patients observed over an average period of 5.2 years at The Mount Sinai Hospital. Special articles are devoted to the changes in blood and bone marrow, to hemorrhagic manifestations, to neurologic and bone complications. The roentgenologic appearance of the small bowel is discussed extensively. The management of malabsorption syndrome is presented with special reference to dietary management, including gluten-free diet, and steroid therapy. The last paper is devoted to an important secondary malabsorption syndrome: the diagnostic and therapeutic problems encountered in patients with extensive resection or exclusion of the small bowel. It was impossible to include all aspects of malabsorption syndrome in the symposium, e.g., there is no comprehensive discussion of celiac disease.

The symposium presents many recent advances in our knowledge of malabsorption syndrome. It is apparent, however, that there are considerable gaps in our knowledge particularly with regard to the basic mechanisms responsible for the disorder. This presents a challenge to all those who are actively interested in this baffling clinical entity.

The Guest Editor is deeply obliged to his colleagues at The Mount Sinai

Hospital, contributors to this symposium, for their unlimited and enthusiastic interest in preparation of the papers. He wishes to express his appreciation to Dr. Cooke in Birmingham and Dr. Shiner in London, the two "extramural" contributors to this symposium, for their willingness to participate in this venture.

The Mount Sinai Hospital
New York 29, N. Y., March 1, 1957

DAVID ADLERSBERG, M.D.
Guest Editor

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THE PHYSIOLOGY OF INTESTINAL ABSORPTION

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It is both appropriate and logical to discuss the physiology of normal intestinal absorption in a symposium devoted to the clinical syndromes of malabsorption. It is doubtful however whether the incomplete state of our knowledge of these processes can at present shed much light on the fundamental defects of the clinical states. Indeed there is reason to believe that unraveling of the pathophysiology of absorption will rather facilitate our understanding of the normal processes. Be that as it may, it is the function of this review to summarize some of the current concepts and hypotheses of absorption from the small intestine.

For this purpose, *absorption* is the process by which materials are transferred from the lumen of the gut through the intestinal mucous membrane to blood and lymph vessels: the transport of nutriment from the exterior milieu to the interior milieu; a process which Fisher and Parsons have neatly labelled *translocation* (1).

In any generally comprehensive schema intestinal absorption represents a special example of the permeability of natural membranes. While some progress has been made towards such comprehensive generalization, the details of which may be found in the monograph of Davson and Danielli (2), the intestinal membrane is such a complex tissue that few overall generalizations can be made with safety at present.

In the regulation of absorption it should be remembered that when materials are presented to the normal intestinal membrane in appropriate form, these are absorbed independent of bodily requirements. There is only one important exception to this statement. Iron appears to be the only nutritive material whose absorption is regulated in keeping with bodily needs (see below). For all other substances it is *intake* and thus hunger and appetite which regulate the quantities absorbed.

Digestion as related to absorption. The main components of the diet are complex, large molecules which do not easily penetrate the intestinal membrane, with few exceptions, and if they do penetrate are poorly utilized. To facilitate absorption, these dietary substances of high molecular weight are broken down to smaller ones which are water-soluble, diffusible, or have active groups by a series of enzymic catalyzed hydrolyses. This preliminary process is properly designated as *digestion* and falls outside the scope of the present review. In the case of fat, however, the role of the digestive secretions, especially bile salts and the lipolytic enzymes, are so intimately concerned with the problem of absorption that some consideration of fat digestion must be included in the discussion of fat absorp-

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tion. Indeed, one of the fundamental not yet completely resolved problems in the field is the extent to which fat, especially triglyceride fat, must be split prior to absorption.

The structure of the membrane. Substances moving across membranes, and the intestinal membrane specifically, fall in the main into two groups: (1) those which move by diffusion according to their concentration gradients, moving from regions of higher to lower concentration, so called passive movement and (2) those able to move against a concentration gradient, a process which requires the expenditure of energy, so called active transport or selective absorption. Further, a substance (such as glucose) may exhibit both kinds of behavior. The cellular mechanisms responsible for the active absorption or transfer of the second group are almost completely unknown, although they are obviously connected with the fundamental structure of the absorbing membrane.

In man, as in most animal species, the main cell of the intestinal epithelium is a cylindrical cell (22 to 26 μ by 6 to 9 μ). Interspaced among these is a mucous secreting cell, the goblet cell. It is not clear whether the mucous secretion forms a continuous surface layer, as is believed to be the case in the stomach.

The free border of the intestinal epithelium, since it is the focal point of transfer, has been the object of histological study for more than a century and only recently is its nature beginning to be clarified. All workers have recognized a striated border at the free surface of the intestinal cell, but opinion has been divided between ascribing a pore-canal system to it or a rod-like tubular structure.

The most careful studies of this border by the light microscope appeared to favor the canal theory (3). However, more recent analyses with the use of the electron microscope have demonstrated that the striated border on the free surface of the absorptive cell is composed of a palisade of columnar rodlets, with blunt rounded tips, closely packed together. The striking electron micrographs of Granger and Baker (4) deserve careful attention from all interested in the fundamental aspects of the process of absorption. These authors have estimated that a single columnar cell must bear nearly 3,000 such rodlike processes, and a square millimeter of intestinal surface some 200 million. Their presence appears to increase the absorptive surface of the gut about 30 fold.

The more recent studies of Sjöstrand and Zetterquist (5) with ultra thin sectioning and electronmicroscopy have confirmed and clarified the nature of the rod-like processes of the epithelial border. This functional increase in surface area is consistent with the other anatomical characteristics of the small bowel: its great length, the mucous folds (Kerkring folds or *valvulae conniventes*) and most strikingly the finger-like reduplication of the mucosa, the intestinal villi. In man it has been estimated that there are 18 to 40 villi per square millimeter of intestinal surface, and an increase of surface area due to the villi of about 7 fold.

Movement of the villi following feeding seems to be clearly established, and there is fragmentary evidence that a humoral mechanism may be involved as well as a local neuro-mechanical one. The significance of this villous movement in the process of absorption however is far from established. An important "pumping" role has been ascribed by Verzar to villous contraction in emptying

the central lacteal of absorbed fat and will be touched upon again in the section on fat absorption.

Methods of research. Progress in revealing the cellular mechanisms involved in absorption has been hindered by the lack of truly physiological methods of investigation. Experiments which involve concomitant studies of intestinal contents and the blood and lymph represent an end result of digestion, translocation, transport and intestinal utilization rather than absorption alone.

Prior to 1925 most of the available information was derived from the study of animals with permanent intestinal fistulas, ligated loops of intestine, by weighing of different parts of the body or by study of histological preparations of mucosa. Then Cori (6) introduced the method of feeding a known amount of substance by stomach tube to rats and killing them after a given period. The amount of the substance remaining in the intestine was then determined quantitatively. This method represented a great advancement and was a source of reliable information.

In 1934 Miller and Abbott (7) first described their double-lumened, single-ballooned tube which was utilized in the study of human absorption. Two years later these same investigators (8) overcame many technical difficulties by the development of a triple-lumened tube with two balloons. These tubes offered a satisfactory method of controlling the site of absorption and length of segment, and, by the introduction of known concentrations and recovery, aided the study of osmotic relationships, motility and their affect on absorption. Others (9, 10, 11, 12, 13, 14, 15) later found modifications of this method of investigation to be fruitful.

Technical methods for research in absorption were then virtually at a standstill until 1949, when Fisher and Parsons (1) described the first *in vitro* apparatus. This consisted of the establishment of two complete circulations, an inner and an outer. The two circulations were separated by a length of animal small intestine such that the inner circulation (mucosal) was completed by the lumen of the intestine, and the outer circulation (serosal) flowed around the intestine. Transfer of a substance from the inner to the outer circulation could take place only by way of the intestinal wall. The success of this apparatus is partially dependent on the feature that the mucosal cells are minimally deprived of oxygen. The structure of the apparatus is such that the physical factors (temperature, pH, solute concentration and concentration gradient) could be controlled.

Other forms of *in vitro* apparatus (16, 17), methods (18), and modifications of these (19, 20, 21, 22, 23) soon followed. The introduction of radio-active isotopes in conjunction with both *in vivo* and *in vitro* studies has been revealing (21, 24). It is from these sources that knowledge of the actual mechanisms, particularly of glucose and amino acid absorption, is slowly evolving.

Progress in the study of fat absorption has been considerably advanced by several technical methods: (1) the introduction of a technique for collecting lymph from the intestinal or thoracic duct in unanesthetized animals by Bollman, Cain and Grindley (25); (2) the development of analytic methods for the estimation of glyceride mixtures and isolation and separation of fatty acids and

phospholipids and (3) the use of isotopically labelled fatty acids, glycerol and glycerides.

FAT ABSORPTION

The mechanism of intestinal fat absorption, an understanding of which is probably central for a complete analysis of the malabsorption syndromes, is a complex as yet incompletely resolved problem, about which much controversy has been collected during the last fifty years. We intend merely to indicate some of the strands of this tangled knot.

Site of fat absorption: From histological studies it has been demonstrated that fat can be absorbed at all levels of the small intestine. What is not known is the site of preferential or maximal absorption. Recently some experimental evidence has suggested that the distal small bowel is more important for fat absorption than the proximal. Kremens and co-authors (26) have demonstrated in the dog that sacrifice of the proximal 50 per cent of the small intestine could be tolerated, but that removal of the distal 50 per cent led to a profound interference with fat absorption. Studies in the rat have indicated that such may be the case in this species as well, the third quarter of the small intestine being most important for fat absorption (27).

The intraluminal phase. It seems clear that neutral fat can be absorbed only if there is hepatic secretion of bile salts and pancreatic secretion of lipase. The bile salts, glyco- and tauro-cholate, appear to have no lipolytic activity themselves but act by emulsifying fat prior to lipase action, thus increasing enzyme substrate contact. Recent studies have shown that these salts function as do other effective detergents by a fat-attracting portion (CH_2 and ethyl groups) and a water-attracting portion (OH , SO_3 or COOH groups). This arrangement results in the formation of micelles in which the hydrocarbon fat-attracting portion lies in the center, and the polar (OH , SO_3 , or COOH) portions on the outside in contact with the surrounding aqueous solution (27A).

In the classical or lipolytic view of fat absorption, promulgated by Pflüger, triglyceride fat in the presence of bile salts and lipase is split completely to fatty acids and glycerol. These products, absorbed in water-soluble form, are then resynthesized in the intestinal cell to neutral fat which enters the lymphatic vessels of the gut and ultimately reaches the venous circulation by way of the thoracic duct. The bile salts return to the liver by way of the portal vein. A great deal of the evidence for this view was derived from the classical observations of Munk and Rosenstein in 1891 on a patient with a lymph fistula of the thigh. A high proportion of fat fed to this patient could be recovered from the fistula, mostly in the form of neutral fat, after ingestion as triglyceride, free fatty acid or amyl esters of long-chain fatty acids.

The lipolytic theory was refined by the studies of Verzar and his collaborators, summarized in their monograph "Absorption from the Intestine" (28). The absorption of fatty acids would be accomplished by the formation of water-soluble complexes with the conjugated bile acids (glycocholic and taurocholic acid) at the slightly acidic pH of the upper small gut. This group of investigators also put

forward the concept that the synthesis of neutral fat from the absorbed glycerol and fatty acids proceeds through an intermediate phosphatide step, under the control of the adrenal cortex. This step involving phosphorylation was believed to be inhibited by high concentrations of phlorhizin and by iodoacetic acid. But the general outlines of the lipolytic hypothesis were essentially unaltered.

A vigorous experimental critique of this theory has been advanced by A. C. Frazer since 1934, to which the term "partition theory" has attached, although this theory too has undergone modification at its author's hand (29). Frazer interpreted his evidence to mean that there are two pathways for fat absorption: (1) highly emulsified particulate neutral fat can be absorbed directly through the intestinal cell to enter the lymph, and (2) fatty acids (derived from lipolysis) enter the portal circulation to be deposited in the liver. A series of studies on the emulsifying action of monoglycerides in the presence of bile salts and on the absorption of highly emulsified paraffin in glyceride mixtures were interpreted as supporting the direct absorption of unsplit fat at particle sizes 0.5μ or smaller.

Recent studies involving newer methods for collecting mesenteric lymph and using isotopically labelled fats and fatty acids have diminished the force of Frazer's partition theory, at least as originally formulated. Bloom and coauthors (30) showed that C^{14} labelled palmitic acid could be recovered to the extent of 92 per cent in lymph, and similar results have been obtained for stearic, palmitic and pentadecanoic acids. These results, which were interpreted as being inconsistent with the partition hypothesis, have been criticized since glyceride vehicles were used for the fatty acid feedings. However, experiments in which free fatty acids were fed have yielded substantially the same results, the only difference being the slower rate of absorption of the free fatty acids as compared with the glycerides. This type of evidence is extremely strong support for the lipolytic theory, and the resynthesis of neutral fat by the intestinal mucosa.

That several mechanisms may be operative however is indicated by two important lines of evidence: (1) Frazer has consistently stressed the point that complete hydrolysis of glycerides to fatty acids and glycerol before absorption is not an obligatory step. Reiser and co-workers (31), and others, recently have shown that some portion (50 per cent or more) of absorbed fat has been hydrolyzed down to monoglycerides but not to smaller molecules. This certainly would seem to indicate that lipolysis need not be complete. This fat, whatever its degree of lipolysis before absorption, is recovered as resynthesized triglyceride fat in the lymph. In this context it is of interest that recent evidence indicates that glycerol liberated during lipolysis is absorbed via the portal system, and utilized for the synthesis of triglycerides or phospholipids in the intestinal cells or contents to only an extremely small extent. (2) Studies in several laboratories have shown that there is a differential partition between the chyle and portal blood as between long- and short-chain fatty acids (2)—fatty acids of 10 carbon atoms or less are absorbed by the portal vein while the longer-chained fatty acids of dietary fat are absorbed by the lymphatics. Thus Bloom and others feeding C^{14} -labelled fatty acids to rats found that 84 to 85 per cent of stearic acid, 59 to 82 per cent of myristic acid, 15 to 55 per cent of lauric acid, and only 7 to 19 per

cent of decanoic acid was recovered in the lymph (32). It is of interest in this context that, of the common dietary lipids, only cows' milk is relatively abundant in shorter-chain fatty acids.

In conclusion, although neutral fat need not be hydrolyzed completely before absorption, the major portion of dietary fat is split to monoglycerides, fatty acids and glycerol in the intestinal lumen in the presence of bile salts and pancreatic lipase. The long-chain fatty acids are absorbed and enter the mesenteric lymph as triglycerides and the short-chain fatty acids enter the portal system as such, along with glycerol.

Cellular mechanisms of fat translocation. Within $1\frac{1}{2}$ to 2 hours after a fatty meal in animals, sudanophilic material can be recognized histologically within the intestinal cell. Whether neutral fat or fatty acids is fed, lipid material can be seen in the striated luminal border of the cell. The mechanism of this passage is not clearly understood at present. At the pH of the intestine (6.7 to 6.8) the fatty acids are probably presented to the membrane in several forms: ionized molecules (RCO_2^-), neutral molecules (RCO_2H), as complexes with bile salts and perhaps as soaps (alkaline salts). Pflüger's original concept that absorption as soaps was the most important mechanism fell into disrepute with the demonstration of the actual pH of the intestine on the acid side of pH 7; yet recent studies by Schmidt-Nelson have indicated that as much as 10 to 25 per cent of the fatty acids could exist as soaps at this pH. The importance of soaps in the problem of calcium absorption will be touched upon below.

Most theories of cell membranes postulate a lipid layer at the surface and these fatty substances could thus easily diffuse into the membrane. What is difficult to explain is their diffusion out of the membrane into the aqueous interior of the cell. Verzar (28) believed that an active process of transport is involved since phlorhizin, which is supposed to inhibit phosphorylation, and monoiodoacetic acid, which inhibits glycolysis, both inhibit the transport of fat across the mucosal cell. In this formulation the fats are transformed into phospholipids in the course of this transfer. It is of considerable interest in connection with the therapeutic aspects of this symposium that Verzar and his colleagues ascribe a regulating function to the adrenal cortex over this stage. In adrenalectomized rats there was a marked impairment of fat absorption. From histologic evidence they concluded that the entrance of fatty acids into the cell continued, but that the resynthesis of fatty acids was inhibited in the adrenalectomized animals. Surprisingly, with the cortical extract of Swingle and Pfiffner (1935) they were able to correct this defect.

Mucosal phospholipid formation during absorption. When labelled stearic acid was fed to rats either as glyceride, free acid, or as cholesterol ester, about 10 per cent of the total lymph fatty acid was recovered in the form of phospholipid (33). There is also available evidence that during absorption of fat, the amount of neutral fat and fatty acid of the gut increases, but the amount of phospholipids remains relatively constant. There are changes, however, in the quantitative fatty acid composition of the intestinal phospholipid depending on the fat being absorbed. This led Sinclair in 1929 to postulate that phospholipids were involved as intermediates in the resynthesis of triglycerides and in the intracellular trans-

port of fatty acids (34). Studies of labelled phosphate have also indicated an increased turnover of the phosphorus portion of phospholipids of the intestinal wall during fat absorption. However, there has been much difficulty in accounting quantitatively for the conversion of all fat to phospholipid during transport, but Bergstrom and Borgstrom point out that it is the phospholipid of the epithelial cell and not of the whole gut which must be involved in this process (35).

The inhibition by phlorhizin of fat absorption is ascribed by some workers not to a specific action on phosphorylation but to inhibition of a variety of enzymatic processes which couple oxidation to phosphorylation in the generation of high-energy phosphate bonds.

In conclusion, the hypothesis that every molecule of fat passes through a phospholipid stage in getting from the luminal to the lacteal border of the intestinal cell remains an interesting but unproved one.

The fine fat particles, having accomplished their passage across the intestinal cell, pass into the lymphatics of the villus. Frazer (29) has stated that this is in accordance with the behaviour of other negatively charged particles which when introduced into the tissues tend to pass into lymphatics rather than blood capillaries. From histological evidence Verzar believes that the muscular contraction of the villi produces a pumping action which tends to empty the central lymph channel and thus move the chyle on. This remains controversial at present. Wells and Johnson (57) deny that shortening of the villi empties the lacteals.

The absorption of other related lipid substances. In the absorption of sterols from the gut specific mechanisms appear to be operative. Cholesterol in the presence of bile salts is readily absorbed. However allocholesterol (an isomer of cholesterol), the four isomers of dihydrocholesterol, coprosterol (a reduction product of cholesterol produced by intestinal bacteria), cholestanol (a tissue reduction product of cholesterol secreted in limited amounts into the gut), as well as phytosterols of plant origin are poorly if at all absorbed. Since all these substances are emulsified by bile, and many diffuse through artificial membranes, it appears that there is marked specificity of the intestinal transport system. Verzar believes that esterification of cholesterol is an essential step in absorption, and that other sterols may not be absorbed because of the absence of appropriate enzyme systems. Under ordinary circumstances the cholesterol presented to the gut is almost entirely free cholesterol, yet a considerable portion of that recovered in the thoracic lymph is in the form of esters. Absorption of cholesterol appears to involve some esterification, and is enhanced by fat as well as bile in the digestive mixture.

In view of the lymphatic transportation of cholesterol, it is puzzling that recent studies appear to indicate that cortisone, hydrocortone and testosterone (not too dissimilar in basic structure from cholesterol) appear to be absorbed from the intestine by the portal venous route. Lecithin appears to be broken down to its constituents which are absorbed as such.

The enterohepatic circulation of bile salts has been discussed already. It is of interest that glycocholates and taurocholates are better absorbed from the jejunum and ileum than from the duodenum.

The absorption of substances dependent on fat absorption, or related to fat absorp-

tion. In this group of substances are the fat-soluble vitamins: A, D, E and K. Vitamin D and its provitamin ergosterol are sterols, while the others are included here because of their solubility in fat and lipid solvents.

1. *Vitamin D*. Although almost all vegetable sterols pass through the intestinal membrane in limited quantities, vitamin D is an exception. The provitamin ergosterol was shown by Schoenheimer not to be absorbed until it is activated by ultraviolet radiation and becomes vitamin D₂ (calciferol). Like other sterols vitamin D requires bile and apparently a certain amount of fat. The exact mechanism of vitamin D absorption is unknown.

2. *Vitamin A*. The absorption of vitamin A and its provitamins, the carotenes, since they are fat-soluble, is determined in great part by the factors determining the absorption of lipids, although it is believed that preformed A and the carotenes can possibly be absorbed without the presence of bile salts. Failure to absorb fat from the gut will lead to a loss of carotenes and vitamin A in the fecal fat, and emulsification of lipid mixtures will improve vitamin A absorption.

3. *Vitamin E*. Although it is not established at present that the tocopherols are essential for man, vitamin E absorption is linked to lipid absorption because of its solubility.

4. *Vitamin K*. Because of its solubility in lipids, vitamin K also is governed by factors which influence the intestinal absorption of fat. Natural K vitamins require bile salts for this absorption, while synthetic water-soluble compounds with vitamin K activity can be absorbed without bile salts.

In general the immediate cellular mechanisms of transfer of these fat-soluble vitamins are unknown. Failure of fat absorption leads to interference in the absorption of these substances presumably because of their solubility in the fats.

Calcium absorption. The intestinal absorption of calcium is also discussed at this point not because the cellular mechanisms of calcium absorption are related to the cellular mechanisms of fat absorption but because disturbances in fat absorption lead to interference with calcium absorption. The major portion of dietary calcium is ingested as calcium phosphate which is difficultly soluble at the pH of the intestine. It is this solubility of calcium which is critical for its absorption since as far as is known only ionic calcium crosses the intestinal cell. A number of factors influence absorption by virtue of their effect on the solubility of calcium salts within the intestinal lumen: a high ratio of phosphate to calcium in the diet will render calcium less soluble, the phytic acid of cereals form insoluble calcium phytate, oxalic acid has a similar effect, while citrates favor absorption by lowering intestinal pH and forming calcium citrate which is relatively soluble.

Protein appears to favor calcium transport presumably due to soluble calcium compounds formed with the amino acids produced by protein digestion. Under conditions of normal fat digestion and absorption the proportion of fat and calcium in the diet appears to have little reciprocal effect on each other. When fat digestion and absorption are defective, calcium forms insoluble calcium soaps with fatty acids and is lost in the stool. In addition, the loss of vitamin D in the steatorrhea also contributes to the inefficiency of calcium absorption.

It has been conclusively established that vitamin D increases calcium absorption from the intestine but the mechanisms are not known. In rats studied with radio-active calcium, absorption occurred during the first 2 to 4 hours after administration, uninfluenced by vitamin D, but after that time vitamin D was necessary for further absorption. Vitamin D causes lowering of intestinal pH, but it is not known whether the vitamin causes a depletion of base in the intestine directly, or whether this is secondary to the increased calcium absorption itself lowering intestinal base.

CARBOHYDRATE ABSORPTION

There is probably more available information on the absorption of sugars than of protein or fats, contributed to no doubt by the relative ease of differential chemical analysis. Though the sequence of events leading from digestion of the various sugars to post-absorptive transportation and utilization is fairly well understood, the details of the selective absorption mechanism are still challenging.

Site of absorption. In natural foodstuffs carbohydrate is found mostly in the form of polysaccharides, especially starch and glycogen. These are in colloidal form but are broken down to glucose by the enzymatic action of diastases. The disaccharides—maltose, sucrose and lactose—are found in lesser quantities, and the hexoses—glucose, galactose and fructose—and the pentoses in respectively small quantities still.

There is practically no absorption of carbohydrate in the stomach, though glucose absorption can take place from this site in the presence of concentrations in the neighborhood of 40 per cent or greater (14, 36). Absorption of sugars by the colon has also been questioned. It has been reported that monosaccharides are not absorbed from the large intestine of the rat or dog (37, 38). The guinea pig, however, can absorb glucose rapidly from a distended cecum, a process not inhibited by phlorhizin, and from other sites in the colon as well when the concentration is 40 per cent or greater (39). At this concentration the translocation of the sugar may be a manifestation of diffusion resulting from damage to the mucosa. Little if any absorption takes place from the human rectum (40).

The main site of sugar absorption is the small intestine. Many investigators have shown that the absorption of glucose is greater in the proximal than in the distal small bowel, though there are conflicting reports as to whether absorption is maximal in the duodenum (42, 43, 44). *In vitro* studies of progressive segments of small intestine reveal that glucose translocation decreases proportional to the distance toward the ileocecal valve, but for technical reasons the duodenum can not be included in this statement (22, 45).

Post-absorptive transportation. Though it has been accepted that the sugar or its metabolites pass directly to the blood stream after translocation, there is evidence that varying amounts appear in the lymph. Information necessary to the solution of this question has been derived, however, from glucose tolerance curves and comparative analyses of reducing substances in both channels, neither method of which is completely satisfactory. Some support for the portal route is derived from the studies of Sherlock and Walshe (46) and others (47, 48) who

noted that superficial anastomotic veins in patients with portal cirrhosis show significant rises in glucose and fructose levels during their respective absorptions, and these levels are higher than that in blood from the antecubital vein.

The influence of concentration on absorption. Hewitt (49), in 1924, studying glucose absorption in rats, reported that the rate of absorption varied directly with concentration. Cori (6), in his classic report a year later, could not confirm this and in fact demonstrated there was no difference in absorptive rates with varying concentration. "Cori's law" was then established that the rate of glucose absorption is independent of concentration. In retrospect, Hewitt was working with glucose concentrations of less than 5 per cent while Cori used concentrations of 25, 50 and 80 per cent. By studying concentrations over both ranges, Groen (12) showed that there was a direct relationship of concentration to absorptive rate up to a 10 per cent concentration, above which the rate was constant, thus clarifying the relationship. There is, apparently, a fixed concentration of glucose (approximately 10 per cent) above which the rate of absorption is constant. Cori (6) showed that, even after absorption of a 70 per cent of a glucose solution from the gut lumen, the rate had not diminished.

In man, Shay et al. (14) demonstrated that the stomach and, to a greater degree the duodenum, are capable of diluting concentrated glucose solutions, and in so doing rendering them isotonic. These same authors (15) later demonstrated that gastric emptying is inhibited proportionally to the glucose concentration. Abbott et al. (50) showed that, regardless of the concentration of glucose ingested, the concentration in the jejunum and ileum is generally less than 5 per cent (isotonic 5.4 per cent). Even if the duodenal and upper jejunal sugar contents are hypertonic, while the lower jejunal and ilial contents are isotonic, the total osmotic pressure of the luminal mixture remains close to 300 mOsm. per L. (isotonic). A concentrated glucose solution in the upper intestine mobilizes a hypotonic fluid gaining volume, while a hypotonic solution loses volume and, concomitantly, there is a decrease in chloride proportional to the rise in concentration of glucose.

The influence of other factors on absorption. A variety of other factors have been reported to influence the rate of sugar absorption. Several components of the vitamin B complex are necessary for the formation of enzymes and co-enzymes of prosthetic groups which are essential to the mechanism of absorption. Althausen (51) showed that a dietary deficiency of vitamin B complex would lead to a decrease in glucose absorption, though xylose transfer was unchanged. Cori and Cori (52) found that rats starved for 48 hours absorbed less fructose than rats starved for 24 hours, while McDougall (28) showed that this was true for glucose also. Westenbrink found that, if an animal was fed with glucose, fructose or galactose for two days or more, its capacity for absorbing the respective sugar was increased (28). It is possible that this adaptation to diet is due to stimulation of specific enzymes in the intestinal mucosa, while the opposite is true with sugar deprivation.

Several endocrine glands appear to influence glucose absorption. Wilbrandt and Lengyel (53) demonstrated that glucose absorption was markedly decreased by

adrenalectomy in the rat, while xylose absorption was not affected. This inhibitory action could be prevented with adrenal cortical hormone. Posterior pituitary extract has also been shown to reduce glucose absorption by 50 per cent (54). Removal of the hypophysis, ovaries or thyroid is followed by a decrease in intestinal absorption of glucose (51). Althausen and Stockholm (55) showed that giving thyroid hormone to normal rats to increase the BMR by 50 per cent could produce a marked increase in absorption of glucose, galactose and xylose.

The influence of physical variations in blood flow through the intestinal wall on absorption is not clear. It can be shown that the quantity of blood flowing through the intestinal wall is much increased during digestion and absorption (28). Evidence has suggested that sugar absorption is related to motility. Cummins and Almy (10) demonstrated this by intubating the upper small intestine and inducing hypermotility with drugs. The mechanism is unknown but may be connected with an increase in the intestinal blood flow. Jones (56) stated that there is an apparent limit to increments in rates of absorption and possibly total absorption as far as motility is concerned. Obviously with markedly increased rates of motility there will be a point at which absorptive processes are decreased, because of decreased exposure of absorbable material to the mucous membrane.

The contribution of villous activity to sugar absorption is also debatable. Though the rhythmic pumping of villi has been observed, the region of greatest activity does not necessarily correspond to the region of greatest glucose absorption (44), and in general there is no correlation between the degree of activity and the rate of glucose absorption (57). Still, Magee and Reid (58) noted that the pumping of villi in the cat's intestine was greatest at 13.5 per cent glucose concentration, the known optimal concentration for glucose absorption in other animals.

There is little information available on the influence of intraluminal pressure on absorption. Nasset and Parrey (59) demonstrated that glucose absorption is independent of intrainestinal pressure between limits of 5 and 25 cm. of the glucose solution below atmospheric. *In vitro* the rate of glucose absorption is proportionately increased up to 10 cm. hydrostatic pressure (22), while with greater pressures there is no change (45).

As early as 1902 Nagano (42) challenged the previously held belief that translocation of a sugar was proportional to its molecular weight by showing that certain six-carbon sugars were absorbed more quickly than five-carbon sugars. He further found variations in the absorptive rates of individual sugars, with galactose, glucose, fructose, mannose, xylose and arabinose being absorbed in that order. Though Nagano's results were disputed for many years, in 1925 they were confirmed by Cori (6). Verzar and Laszt (1935) further distinguished between glucose and galactose—which seemed to be absorbed at a constant rate regardless of concentration—and xylose, sorbose and mannose—whose rate of absorption was related to concentration (28). These authors first suggested that there was an active process involved in the absorption of certain sugars. It had been discovered earlier that there is mutual inhibition of absorption of glucose

and galactose; the total amount of both absorbed is no more than if only one is given (60). This suggested that both are absorbed by the same process and that there is a limiting factor other than the total amount of sugar present and their concentrations.

That glucose, galactose and fructose are absorbed by a selective and specific mechanism was clearly demonstrated in later years. Fisher and Parsons (45), Wilson and Wiseman (18, 61), Darlington and Quastel (16), Korelitz and Frank (22), and Wilson and Vincent (62) all showed that aerobically glucose is transferred against a concentration gradient while anaerobically (or when oxygen is replaced by nitrogen) the glucose transfer is equivalent to that expected by diffusion alone. Galactose and fructose are also transported aerobically against a concentration gradient. Fructose absorption differs from the other two, however, in that glucose appears in the outer solution in much greater quantities than fructose. The small amount of fructose that is transferred as fructose can be accounted for by diffusion alone. Mannose, sorbose, xylose, arabinose and ribose are not transported against a concentration gradient; their transfer is directly proportional to concentration. There is apparently no selective mechanism for their transport.

That an active respiratory system is essential for the selective absorption was shown not only by the inhibiting influence of anaerobiosis, but also by the inhibitory effects of phlorhizin, monoiodoacetic acid, 2,4-dinitrophenol, cyanide, azide, fluoroacetate, malonate and chloretone (16, 45, 63, 64). Diffusion of sorbose or, fructose is not altered by these. The nature of this selective mechanism remains to be elucidated.

Phosphorylation theory. When it was shown that the addition of a phosphate buffer at pH 7 increased the rate of glucose absorption in rats, the theory was initiated that glucose might be transformed into a phosphate compound in the mucosa during absorption (58). Though it was later shown that the accelerating action of the phosphate was a pH effect (65), further investigation was stimulated.

It is known that both mono-iodoacetic acid and phlorhizin inhibit phosphorylation and they also hinder glucose and galactose translocation in the intestine (28, 45, 63, 64, 66, 67). It has also been demonstrated that organic phosphate increases in the mucosa during glucose absorption (68, 69). With this indirect evidence and the knowledge that phosphorylation played an important part in the intermediary metabolism of glucose elsewhere, a similar mechanism was felt to be active in glucose and galactose absorption. The phosphorylation theory then explained selective absorption as dependent upon the conversion of the hexose within the epithelial cell of the intestinal mucosa to a hexose phosphate. Since there would be no unconjugated free glucose or galactose within the cell a steep gradient is obtained which favors the continuous translocation across the epithelial membrane.

The phosphorylation theory has been challenged on many occasions during the past few years. No significant change in concentrations of several acid-soluble phosphate fractions was found in the mucosa when the glucose absorptive rate

was altered by influencing thyroid activity (70). There was no difference in the phosphate content of various areas of mucosa which are known to absorb glucose at different rates. It was also shown *in vitro* that the presence of phosphate is not necessary for active glucose absorption (16). Evidence was presented that mono-iodoacetic acid and phlorhizin were general tissue poisons and do not act specifically by inhibiting phosphorylation but more likely interfere with the utilization or coupling of energy bonds (64).

A great deal of support for the phosphorylation theory stemmed from experiments in which the inhibited selective absorption of glucose and galactose was compared to the uninhibited diffusion of xylose. Davidson and Garry (71) showed, however, that xylose is absorbed as rapidly as glucose from the distal small intestine of cats, emphasizing the problem of species differences. To further challenge the theory that all pentoses were absorbed by diffusion, it was shown that xylose and mannose are also phosphorylated (72, 73). Studying homogenates of rat intestine, Sols (73) compared the rates of absorption of many sugars with their rates of phosphorylation and found a serious lack of correlation between the two.

Although the evidence suggests that phosphorylation is involved in the transfer mechanisms for sugars, there is no proof of its exact role in active absorption.

In vitro studies of active mechanisms. The results of *in vitro* studies have raised an alternative explanation for selective sugar absorption. Hestrin-Lerner and Shapiro (21) reported that 30 to 60 per cent of glucose disappearing from the perfusing mucosal solution could be identified as a non-reducing substance in the serosal solution. Further investigation *in vivo* revealed that during absorption the concentration of radio-active material was higher in the portal vein than in the aorta, though the concentration of radio-active reducing substances was less (24). A considerable amount of radio-activity associated with a non-fermentable substance was found in the intestinal wall as well. They proposed that a non-fermenting glucose metabolite is formed in the intestine during glucose absorption and passes to the portal blood as such, the process maintaining a high concentration gradient for glucose between the lumen and the cell.

This theory is disputed in that other investigators have found considerable amounts of lactic acid in the serosal solutions which could represent the unidentified non-fermenting metabolite described above (18, 74). Still others (17, 22, 45) have identified glucose as such in the serosal solutions, suggesting that the whole question of the metabolite theory is artifactual and attributable to inadequate oxygenation of the intestinal mucosa.

Absorption of fructose and sucrose. *In vitro* studies have revealed that fructose is converted to glucose in the process of absorption, any transfer of fructose as such being attributable to diffusion (16, 75). Since diffusion is proportional to concentration, it is understandable that with large concentrations of perfusing fructose solutions, more fructose will be transferred without conversion to glucose.

Sucrose is partially broken down within the intestinal wall and appears on the serosal side as glucose and fructose as well as sucrose (75). As with fructose perfusion, the amount of sucrose translocated as such is proportional to concentra-

tion. With increasing concentration the percentage of perfusing sucrose translocated as glucose will fall, while that translocated as sucrose rises and fructose remains constant.

In summary, it is well substantiated that sugars are absorbed predominantly from the small intestine, more in the proximal than the distal, and that above a concentration range of 10 to 13 per cent the rate of absorption is independent of concentration. The presence of a selective mechanism for the absorption of glucose, galactose and fructose has been verified, while in contrast other monosaccharides are translocated according to simple physical laws. The exact nature of the selective mechanism has in no way been clarified. Though phosphorylation is involved in the process in some manner, evidence has not supported this as the entire explanation. A better understanding of the interrelationships and influences of the hexokinase and other enzyme systems will probably be necessary for the final solution.

PROTEIN ABSORPTION

Until recently information on the mechanism of protein absorption was scanty. In the 19th century it was assumed that protein was absorbed as peptones and proteases. Later all the known amino acids were discovered in the intestine during absorption (76) and the identification of enzymes which split peptones and the proteases rounded out the picture (28).

Though it is recognized that proteins are absorbed as amino acids there have been suggestions that protein is also absorbed in larger forms. Though the impermeability of the intestinal mucosa for colloidal particles makes the absorption of polypeptides unlikely, the appearance of various naturally occurring proteins in the portal blood and especially the lymph has been found in the investigation of allergic phenomena (77, 78). It has been further argued that some protein complexes must get through as indicated by the functional integrity of ingested thyroid extract. Theoretically dipeptides should then be transferred more easily. There is some evidence that these are absorbed in small quantities but never to a marked degree (19, 79).

Site of absorption. There is little evidence that protein is absorbed at any other site than the small intestine, though absorption by the stomach has been reported by many earlier workers (28). It has been suggested that under physiological conditions the products of digestion leave the stomach too quickly for absorption to take place there. Amino acids are almost entirely absorbed in the small intestine; if any enter the large intestine they are probably absorbed to a small extent but are partially destroyed by bacteria. Amino acids probably diffuse through rectal mucosa as well (80). *In vitro* study has revealed that alanine is absorbed to a greater extent in the jejunum than in the ileum (22). After translocations of the amino acids they are transported in the portal system and to a lesser degree in the lymph (28, 81). When larger forms of protein are absorbed they are found predominantly in the lymph (78).

Influence of concentration on absorption. The effect of amino acid concentration on absorption is not as well established as in the case of glucose. *In vitro* the rate

of appearance of alanine in serosal solution is proportional to its concentration in the intestinal lumen. (82). The greatest rate of increase occurs over a range of low concentrations above which the absorptive rate is constant. In this regard amino acid absorption would be similar to the selective absorption of sugar. It has been suggested that a saturation of the intestine with the amino acid is necessary before any is translocated (19) or that saturation is the limiting factor in absorptive rate (82). It would seem reasonable that saturation is the limiting factor in rate of absorption, but transfer of amino acid would occur at increasing rates proportional to increasing concentration until saturation is reached.

Selective mechanisms. Just as with glucose the absorption of amino acids had until recently been considered by most workers in the field a matter of simple diffusion (81, 83). After Hober and Hober (1937) (84) emphasized that there was an active mechanism for amino acid absorption, many authors were able to demonstrate by various techniques that in racemic mixtures of an amino acid the *L*-isomer is transferred more rapidly than the *D*-isomer, with which the rate is consistent with diffusion alone (85, 86, 87, 88). With the introduction of *in vitro* method many workers were able to show that the *L*-isomer of methionine, alanine, phenylalanine, histidine, isoleucine, glycine and proline could be translocated against a concentration gradient, while the *D*-isomers could not (17, 19, 61, 89, 90). This active transfer could be blocked by anaerobiosis, cyanide and dinitrophenol but not by phlorhizin (19, 22, 82). Kuroda and Gimbel (91) showed that the disappearance of the *L*-isomers was greater than that of the *D*-isomers from an *in vivo* loop of human intestine.

Other amino acids including glutamic acid, aspartic acid, lysine and ornithine are not actively transferred (17, 19, 90). The glutamic or aspartic acid lost from the intra-luminal space could not be recovered from either the outer solution or the intestinal wall (17). When glutamic acid alone was perfused through both the inner and outer solutions, the presence of alanine was discovered in both solutions, the outer more than the inner, at the end of the test period. When aspartic acid alone was perfused, both alanine and glutamic acid could be found in the outer solution. When other amino acids were perfused individually the transfer of only that specific amino acid as such could be demonstrated.

As with the hexoses competing for the common selective mechanism of absorption, mutual inhibition has been demonstrated for amino acids (90, 92). Some actively transported *L*-amino acids when perfused alone were transferred at comparatively low rates (methionine and histidine). When perfused in combinations these would hinder the transfer of other amino acids (proline and glycine) which would individually be transferred at a comparatively high rate. The *L*-amino acids not moving against a concentration gradient (glutamic, lysine and ornithine) had no effect on the transfer of amino acids for which there is an active mechanism. Those that are transferred at a rapid rate did not hinder those that are more slowly transferred. Kamin and Handler (93) performed experiments which showed that this competition was of little consequence in comparison to that exerted in the renal reabsorption of amino acids.

Phosphorylating processes have been implicated as in selective carbohydrate

absorption. Since phlorhizin inhibition is one of the mainstays of the phosphorylation theory of carbohydrate absorption, the failure of phlorhizin to inhibit selective amino acid absorption is a telling argument.

To summarize, amino acids are absorbed predominantly by the small intestine and it appears that as with glucose there is a limiting concentration above which the absorptive rate is constant. The presence of a selective mechanism for amino acid absorption is verified by experiments showing that there is translocation against a concentration gradient and the preferential absorption of the *L*-versus the *D*-isomer. Even among the *L*-isomers it appears that the mono-amino-mono-carboxylic acids are transferred while the di-amino acids (lysine, ornithine) are not, demonstrating selectivity in the active mechanism. Evidence suggests that while glutamic acid and aspartic acid are not actively transferred, they are involved in a trans-amination process, although they are probably partially metabolized as well.

The intricate nature of the active and selective mechanism is not understood but again is probably intimately associated with specific enzyme systems and utilization of energy.

WATER ABSORPTION

Site. Water is probably absorbed from all sites in the gastro-intestinal tract. Though early studies could not demonstrate absorption from the stomach, it is now suggested that up to 2.5 per cent of administered D_2O may be absorbed per minute from this site (95, 96, 97). Considerable water absorption from the colon has been established (28). The main site of water absorption is the small intestine where Lee et al. (97) showed a water loss of 23 per cent per minute.

Hormonal and mercurial influence on water absorption. In general water translocation *per se* is not influenced by hormones except passively as its solutes are affected. Pitressin, however, produces a significant increase in the absorption of water from isosmotic saline, though this is not necessarily of physiologic significance (98). Addition of mercurhydrin to test solutions in the gut is accompanied by decreased rates of absorption of sodium, chloride and water, an effect which is decreased with repeated use of the drug (99). This suggests a similarity between intestinal mucosa and renal epithelium in this respect. A similar result follows the administration of $HgCl_2$.

Mechanism of water absorption. Water transfer between blood and intestinal lumen is influenced by so many other factors that the presence of a selective mechanism for this purpose is questionable. To confirm the presence of a selective mechanism it would be necessary to demonstrate an accelerated transfer of water beyond that expected by diffusion and independent of ion transportation.

Early experiments demonstrated the basic prerequisites that permeability for water occurs in both directions across the intestinal wall (28), that crystalloids diffuse from gut to blood, according to their diffusion velocities (100, 101, 102, 103) and that crystalloids can at least enter the intestine from the blood (104, 105). It was shown in both animal and human experiments that the osmotic pressure of intestinal contents becomes equal to that of the blood by virtue of water and electrolyte shifts which were considered to take place according to the phys-

ical laws of diffusion and osmosis (12, 50, 101). Further support for this was given by Verzar and McDougall (28) who showed that a solution of selectively absorbed glucose becomes isotonic before water leaves the intestine, while from a passively absorbed xylose solution the xylose will diffuse into the blood and be replaced by blood crystalloids with resulting maintenance of isotonicity but no water absorption.

Not all investigators have accepted the transfer of water according to simple physical laws. Vischer and his co-workers (106, 107) showed that univalent ions can be concentrated in the intestine to levels above the blood concentration, a process which could be hindered by the presence of other anions or cations of valence greater than one. The lowering of the univalent ion concentration in the lumen would have to be accompanied by diffusion of this ion against a concentration gradient, requiring osmotic work. It was also shown in D_2O experiments that while the concentration of chloride ion moving out of the lumen is proportional to the concentration in the lumen, the apparent concentration of chloride moving into the lumen is practically independent of its concentration in the blood (108). Such being the case, the luminal solution should become hypotonic and influence water absorption in this way. This school later showed in calculating the ratio of total directional rates (blood to gut and gut to blood) to net transport rates of water that there was a 200 fold difference between that derived experimentally and that expected on the basis of diffusion (109).

Another school has suggested that water is transported neither by simple physical laws nor by an active mechanism but rather as an obligatory carrier of a selectively absorbed substance. Wilson and Wiseman (18) showed that the translocation of water in the presence of glucose or methionine is inhibited by anaerobiosis. In the *in vitro* apparatus with glucose solution on the mucosal side and bicarbonate solution without glucose on the serosal side, translocation of water (along with glucose) continues contrary to what would be expected by osmosis (110).

A few words should be devoted to the influence of colloidal osmotic pressure and hydrostatic pressure on water transfer. Each of these factors has been proposed to explain the translocation of both the water and its solutes after isotonicity has been established within the lumen. Such explanations would be necessary if water were considered transported by simple physical laws. According to "Starling's Law," though the concentration of diffusible solutions on either side of the intestine must be equal, the plasma colloids have a higher osmotic pressure than the colloids of the intestinal solution and water must then pass into the blood. The resulting increase in salt concentration in the lumen would be followed by a diffusion of salts into the blood.

It has been reported that water absorption increases as a linear function of pressure (111), though *in vitro* studies disprove this for pressures greater than 10 cm. in animal intestine (1). It is known, however, that the colonic pressure may rise to as high as 40 cm. of water (28), possibly explaining the almost complete absorption of isotonic solutions from this site. The presence of large amounts of fluid in the small intestine, by increasing the hydrostatic pressure, might exert an influence there as well.

In summary, though the means of water absorption is not at all clear at present, it appears that there is no active mechanism for this purpose. There is, however, an active mechanism for the absorption of electrolytes. The electrolytes pass from the lumen to the blood according to diffusion velocities and osmotic laws, while the passage from blood to lumen is much more complex, probably influenced by multiple factors. It is the latter mechanism that is responsible for active electrolyte absorption, while water absorption is influenced secondarily. The organic solutes for which there is a selective absorptive mechanism will, during their transfer, also carry an obligatory amount of water. Colloidal osmotic and hydrostatic factors probably physically influence water transfer but are minor factors in net transport.

IRON ABSORPTION

Though this subject has been adequately and frequently reviewed (112), discussion of the specific mechanism involved in iron absorption is pertinent for an understanding of absorption in general. It is well recognized that iron must be present in the ferrous form in order to be absorbed. In natural foodstuffs iron is mostly contained as ferric hydroxide or ferric-organic chelates (citrate, lactate, amino acids). Both hydrochloric and organic acids serve to break down the iron compounds to ferric ions or loose ferric chelates which can be readily reduced to ferrous ions by such reducing agents as ascorbic acid and sulfhydryl compounds present in food.

Since iron once absorbed is almost completely retained by the body, some mechanism for iron regulation must exist to prevent excess absorption but still permit adequate amounts to be absorbed. This mechanism is known to exist along the entire small intestine, though the region of most active absorption is the first part of the duodenum. Chronically anemic dogs were found to absorb iron at a rate of 5 to 15 times greater than normal (113). This response would not follow a sudden bleeding but would occur only after several days, suggesting a correlation between iron absorption and iron reserves in the body. After administration of iron, the degree of resistance to further absorption could be shown to increase rapidly for several hours, and remain constant for several days, then gradually decline. Hahn et al. (113) suggested that there was a mucosal block which was probably explained by a temporary storage of iron.

Granick (114) then described the presence of ferritin crystals, consisting of clusters of ferric hydroxide attached in four discrete areas to a protein, in the small intestinal mucosa, especially the duodenum. Several hours after a single iron feeding the increased concentration and the distribution of the ferritin crystals remained constant, and after the maximum iron feeding it would take six days before the mucosal ferritin content would approximate normal. He reasoned that the involved protein (apoferritin) was constantly produced and broken down in the mucosal cells but, if protected by adhering ferric hydroxide clusters forming ferritin, it would accumulate. It would follow that ferritin should increase in response to iron feeding. The time sequence of the change in ferritin content in general paralleled that of the appearance and disappearance of the mucosal block.

Ferritin has been demonstrated in both fixed tissue histiocytes and the colum-

nar epithelial cells. In the tips of duodenal villi, Granick (114) found histiocytes containing yellow or green vacuoles. After a few days of iron feeding, the vacuoles and associated granules in the histiocytes would stain dark grey to black. The granules were sometimes observed in the columnar cells. Granick suggested that the columnar cells may be the site of origin of the ferritin while the histiocytes function primarily as a protective mechanism by taking up excess amounts of iron into their vacuoles.

The means by which iron absorption proceeds from the stage of intra-mucosal ferritin is not clear. A protein (transferrin, siderophilin) has been identified which serves to transport iron in an Fe-transferrin complex. It is likely that transferrin picks up the iron as it leaves the mucosal cell, though this one step has not been demonstrated. It has been shown that the rate of movement of iron from the mucosal cells into the blood stream is independent of the degree of transferrin saturation with iron. A lowered oxygen tension, however, has been correlated with an increased rate of removal of iron from the cells. Granick (114) suggested that the iron leaves the ferritin complex and the mucosal cell in ferrous form where it is immediately auto-oxidized to the ferric state and transported away attached to a specific component of the globulin fraction (transferrin or otherwise). This explanation would require a preliminary step of reduction of the ferric iron of the ferritin.

It appears that both the mucosal block and the completion of iron translocation involve a complicated series of iron oxidation and reduction reactions. The physiologic mechanism of ferrous iron saturation, the influence of storage and serum iron on the absorptive rates, the uni-directional movement of the iron in the epithelial cells and the form and means of transfer from the cell to the portal system are yet to be explained. It has been proven that the iron is transported by the portal blood and not by the lymph (115, 116, 117).

There is no strong evidence that organ systems other than the pancreas influence the absorption of iron. It has been shown that ligation of pancreatic ducts will promote an increased deposition of iron in the liver (118, 119, 120), though this has not been shown to be true in all animal species. The mechanism is not understood.

SUMMARY

It seems clear that the products of digestion of the major food stuffs of the diet, and the accessory food factors (electrolytes, vitamins) are absorbed across the intestinal cell by selective processes of active transport, which require the expenditure of energy and spatially orientated enzyme systems. The details of these intracellular processes of translocation are almost completely unknown at present.

Absorption of neutral fat requires the hepatic secretion of bile salts and the pancreatic secretion of lipase, and occurs throughout the entire small intestine, perhaps to a greater extent in the distal half. Neutral fat need not be hydrolyzed completely before absorption, but the major portion of dietary fat is split to monoglycerides, fatty acids and glycerol in the intestinal lumen. Long-chain fatty acids appear in the mesenteric lymph as triglycerides, short-chain fatty

acids enter the portal vein as such along with glycerol. Active transport of lipid across the intestinal cell is involved in this process, but the details are obscure. The role of phosphorylation in this translocation is not fully established.

Carbohydrates are absorbed predominately as monosaccharides and more by the proximal than the distal small intestine. Above a concentration range of 10 to 13 per cent, the absorption rate is independent of concentration. This is of little importance under physiological circumstances, however, since inhibition of gastric emptying and dilution of concentrated solutions in the duodenum serve to render solutions isotonic. A selective mechanism for the absorption of glucose, galactose and fructose has been verified while other monosaccharides are translocated passively. A phosphorylation theory has been offered to explain the selective absorption, and though phosphorylation is involved, it does not appear to be a complete explanation. *In vitro* studies have opened new fields of investigation in carbohydrate absorption, and some new light has been shed on fructose and sucrose transfer.

Protein is absorbed predominately as amino acids, and again there is a limiting concentration above which the absorptive rate is constant. The presence of active and selective mechanisms for amino acid absorption is confirmed by the demonstration of intestinal transfer against concentration gradients and by preferential absorption of the *L*-isomer. Among the *L*-isomers the mono-amino-monocarboxylic acids are transferred while the di-amino acids are not.

It appears that there is no demonstrable active mechanism for water absorption but there is one for electrolytes. While the latter pass from intestinal lumen to blood according to diffusion velocities and osmotic dictates, movement in the opposite direction is more complex. Water transfer is dependent on electrolyte transfer and the selective absorption of organic solutes. Colloidal, osmotic and hydrostatic factors are of less importance in net water transport.

The mechanism for iron absorption is unique in that the amount absorbed is controlled by the body's need. The present knowledge of the apoferritin-ferritin process in the mucosal mechanism and subsequent completion of iron absorption are reviewed.

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DISTURBANCES IN PROTEIN AND LIPID METABOLISM IN MALABSORPTION SYNDROME

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The malabsorption syndrome (idiopathic sprue) is a complex metabolic disorder in which multiple defects of intestinal absorption form an integral part. Steatorrhea and emaciation are important clinical features. It has previously been established that the sprue syndrome is associated with hypoproteinemia and hypolipidemia (1-6). In a study of the characteristic features of this disorder in a selected group of 94 patients, several were encountered in whom isolated deficiencies of serum proteins and lipids suggested the presence of a more profound disturbance in protein and or fat metabolism. In the majority of the patients data concerning serum proteins and serum lipid partition were collected during acute relapse and during periods of clinical control. A detailed presentation of these laboratory data, together with a correlation with clinical symptoms and therapy, was therefore undertaken. In addition, three illustrative cases are present in detail.

The group consisted of 32 men and 62 women whose age averaged 45 years. The mean duration of symptoms prior to first hospitalization was 7.2 years. The follow-up period averaged 5.2 years. A detailed study of the symptomatology and signs of these patients is presented elsewhere in this symposium (7).

SERUM PROTEINS IN THE MALABSORPTION SYNDROME

Determinations of serum proteins by the biuret method (8) were performed in 67 patients. The mean level was 5.7 gm. per cent (range 3.6 to 8.5). In 19.4 per cent of the cases the total protein concentration was below 5.0 gm. per cent. Serum albumin, determined by the same method in 60 patients, ranged from 1.4 to 5.3 gm. per cent with a mean concentration of 3.3. In 51.8 per cent of the cases the serum albumin level was below 3.5 gm. per cent. In 23.4 per cent the level was lower than 2.5 gm. per cent.

In 16 patients a considerable degree of dependent edema was present at the time of hospitalization. In this group the mean total protein concentration was decidedly lower, averaging 4.8 gm. per cent. Serum albumin levels were similarly depressed to an average of 2.4 gm. per cent. These findings suggest that edema in sprue is usually correlated with hypoproteinemia, in particular with hypoalbuminemia. Two of the 16 patients had ascites in addition to dependent edema; their total protein levels were 3.1 and 4.3 gm. per cent, while serum albumin concentrations were 1.7 and 1.9 gm. per cent.

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The over-all depression of serum total proteins, including both albumin and globulin, suggests that there is impaired synthesis of these components. This may be a result of deficiency in precursors due to inadequate intake, impaired absorption of protein, loss in the stool, and impaired synthesis by the liver due to effects of malnutrition or as part of the general metabolic disorder. Serum albumin is affected to a greater degree than the globulins, as reflected by the more marked depression in levels of this protein fraction.

It is of interest that the levels of serum globulin in the total group of patients were the same as those with edema. In the former the average was 2.4 gm. per cent, while in the latter the average was 2.3. These levels are somewhat depressed, suggesting that there is an impairment of globulin formation in sprue. However, this is not necessarily correlated with the clinical severity of the sprue syndrome, is not responsible for the drop in total protein and is not correlated with edema.

A further investigation of the serum protein pattern and globulin distribution in patients with sprue was undertaken. Other investigators had described the occurrence of a sprue-like syndrome in patients with agammaglobulinemia (9).

TABLE I
Serum protein patterns in idiopathic sprue

Case No.	Sex	Age	Paper Electrophoresis					Chemical Analysis		
			Albumin	Alpha-1	Alpha-2	Globulins	Gamma	Total Protein	Albumin	Globulin
			Per cent of total	Beta	stainable	protein				
1	F	42	36.9	7.7	15.4	13.3	26.7	6.8	3.9	2.9
2	F	35	51.4	10.8	8.1	10.8	18.9	7.2	5.1	2.1
3	F	71	40.7	5.3	11.2	19.1	23.7	7.5	4.5	3.0
4	F	48	50.8	4.7	10.1	11.7	22.7	7.2	4.5	2.7
5	F	43	44.9	11.8	12.6	11.8	18.9	6.4	3.9	2.5
6	M	38	46.5	5.1	8.5	17.0	22.9	7.2	4.0	3.2
7	M	67	36.0	6.2	16.4	23.4	18.0	5.4	3.3	2.1
8	F	65	46.9	5.0	15.0	13.7	19.4	7.5	4.5	3.0
9	M	54	38.9	6.4	18.3	18.3	18.1	4.4	2.5	1.9
10	F	44	50.0	5.6	10.0	19.4	15.0	6.0	4.0	2.0
11	F	48	45.1	8.4	18.3	18.3	19.9	4.8	2.7	2.1
12	M	26	37.5	7.1	13.8	18.7	22.7	7.5	4.5	3.0
13	F	46	38.7	12.7	8.7	21.0	19.1	6.2	3.8	2.4
14	F	62	48.2	5.4	12.1	17.5	16.8	7.2	4.4	2.8
15	F	62	44.0	7.7	17.6	12.0	18.7	6.7	4.6	2.1
16	F	69	32.6	9.8	18.5	20.6	18.5	6.3	3.3	3.0
17	M	57	49.6	6.2	13.8	9.7	20.7	5.7	3.5	2.2
18	F	36	53.7	3.6	10.5	10.5	21.7	7.0	3.9	3.1
19	F	63	34.6	6.0	13.8	23.0	22.6	7.5	3.9	3.6
20	M	67	40.7	4.7	14.0	12.3	28.3	7.7	3.8	3.9
Mean			43.3	6.9	13.2	16.0	20.6	6.7	3.9	2.7
Normal			52.5	4.2	12.2	14.0	17.1	7.5	4.5	3.0
S.D. \pm			3.7	1.5	3.6	2.9	3.0			

Therefore, the sera of 20 patients with idiopathic sprue were subjected to paper electrophoresis using a method previously described (10).

A horizontal apparatus with free suspension of the paper strips was employed, using a Veronal buffer at pH 8.6, ionic strength 0.05. After application of 0.007 ml. of serum, a potential of 250 volts was applied for 6½ hours with a current of 2.5 milliamperes per strip. The paper strips were then stained with Amido-black after drying at 70°C. The patterns were read in a photoelectric densitometer and the curves derived were evaluated planimetrically. Five components were determined: albumin, alpha-1, alpha-2, beta and gamma globulins. Simultaneously, total protein, albumin and globulin were determined chemically (biuret method).

The data from the individual patients is presented in Table I. Albumin levels were low, and those determined electrophoretically were even lower than those determined by the ordinary chemical method. The lowest levels were obtained in patients who were seriously ill. In this group of patients no instances of agammaglobulinemia were noted and generally gamma globulin was increased. There was also a tendency to increased levels of beta globulin which was marked in some instances. There was little change in levels of alpha-2 globulins and an increase in alpha-1 globulin. These apparently non-specific globulin alterations indicate that serum globulin levels are maintained at absolute levels which approximate those in normal sera, while serum albumin is below normal.

In one patient, on repeated examinations, electrophoresis of the serum yielded a spike in the gamma globulin region similar to that observed in patients with multiple myeloma. Bone marrow and roentgen examinations failed to yield evidence of any blood dyscrasia. No macroglobulins were present in the serum.

INTRACTABLE HYPOPROTEINEMIA AND EDEMA AS PROMINENT FEATURES OF IDIOPATHIC SPRUE

The following two patients, observed over a period of 12 and 17 years, respectively, are presented to illustrate hypoproteinemia and edema as leading clinical features of sprue.

Case 1

A 21 year old girl was hospitalized in 1932 because of progressive leg edema of five months duration. Six months before she had had a tonsillectomy which was followed by four or five post-operative hemorrhages. Shortly thereafter she developed anorexia, postprandial abdominal pain and weakness. On examination she appeared pale and her blood pressure was 102/50. There was pitting edema of the lower legs. The hemoglobin was 11.9 gm. per cent. Urinalysis was negative. The total protein was 5.2 gm. per cent with albumin 3.6 and globulin 1.6 gm. per cent. A diagnosis of static edema and psychoneurosis was made.

She was hospitalized eight months later with persistent edema and pain in the left flank and leg. An intravenous pyelogram was negative. The diagnosis of sacro-iliac arthritis was made.

She was hospitalized again in 1935 at age 24 years. In the interval she had intermittent ankle edema and fatigue. She also developed tetany, abdominal pain and diarrhea. She had been hospitalized elsewhere where pigmentation of the skin was noted. Hypoproteinemia (3.3 to 5.8 gm. per cent) persisted. Serum calcium level was 7 mg. per cent. Roentgen exam-

ination of the gastrointestinal tract was reported to be normal. She developed acute intestinal obstruction due to incarceration of a post-appendectomy ventral hernia which was repaired. Five weeks before admission severe diarrhea recurred with abdominal pain, vomiting, anorexia, progressive low grade fever, weakness and paresthesias. She was emaciated and pale. The abdomen was diffusely tender and doughy. There was free hydrochloric acid in the gastric contents. Total protein was 5.4 gm. per cent, albumin 3.1. The glucose tolerance curve was flat. Barium enema revealed redundancy of the sigmoid and dilatation of the colon. Following a barium meal there was patchy distribution in the small intestine. The patient improved but ambulation was followed by recurrence of edema. There were two episodes of tetany; serum calcium was 6.8 mg. per cent. She also developed glossitis. She was treated with a high protein diet, calcium and viosterol. Edema persisted and blood proteins remained 4.8 to 5.2 gm. per cent.

At this time the diagnosis of non-tropical sprue was suggested. She was treated with diet, liver extract, calcium and vitamins and thereafter she gained weight. The edema diminished but continued to recur. Bouts of diarrhea persisted and were accompanied by tetany and paresthesias.

She was hospitalized again eight years later (1943). She had lost 17 pounds during that period. The blood pressure was 90/68. There was no edema. Hemogram was normal. Total serum protein concentration was 4.3 gm. per cent and albumin was 2.3 gm. per cent. Serum calcium concentration was 6.3 mg. per cent. Duodenal drainage showed normal pancreatic enzymes. Vitamin A and glucose tolerance tests revealed flat curves. Fecal fat content was 21.4 per cent of dry weight. X-ray of the small intestine showed dilatation and segmentation. She received a high protein diet, plasma, amino acid infusions, vitamins and calcium. Total serum proteins rose to 5.8 gm. per cent and calcium concentration to 10 mg per cent. The diarrhea diminished.

She was hospitalized again four months later at age 33 years (1944) for diarrhea, tetany, abdominal cramps and fever. Chvostek and Trousseau signs were present. Total serum proteins were 6.0 gm. per cent and the albumin was 3.6 gm. per cent. There was a prolonged Q-T interval in the electrocardiogram. She improved only temporarily on a regimen of diet, liver extract, vitamins and calcium. Symptoms persisted until her final admission four months later. She appeared emaciated (weight 91 pounds). There was moderate clubbing of the fingers. Microscopic examination of the stool revealed large amounts of fat. On roentgen examination there was marked dilatation of the small intestine with loss of mucosal pattern and segmentation. Serum albumin was 2.5 gm. per cent and globulin was 1.5 gm. per cent. Serum calcium concentration was 8 mg. per cent and alkaline phosphatase was 31 King-Armstrong units. Therapy included diet, liver extract, pancreatin, vitamins and calcium as well as plasma, whole blood and AT-10. Her course was steadily downhill. She died suddenly with tetanic convulsions one month after admission. Post-mortem examination revealed thromboses of the dural sinus and cerebral veins, visceral atrophy, fatty liver and distention of the intestine (11).

Comment: A young woman had hypoproteinemia and edema which persisted over a period of years. Tetany and hypocalcemia were prominent clinical features. Diarrhea and evidence of malabsorption were subsequently present. Symptoms continued despite vigorous therapy. The patient died 12 years after the onset of the disorder.

Case 2

A 54 year old white man had leg edema of varying degree beginning at the age of 27 years (1930). He had repeated episodes of erysipelas and cellulitis involving one or both legs since 1938. He was hospitalized four times from 1938 to 1945. During this period, there was constant hypoproteinemia which was considered the cause of the persistent edema. The serum

total proteins ranged from 3.1 to 5.5 gm. per cent, with serum albumin ranging from 2.2 to 3.8 gm. per cent and globulin 1.1 to 1.9 gm. per cent. No cause for the hypoproteinemia could be found despite extensive investigation. Roentgenologic study of the small intestine in 1938 revealed hypomotility and evidence of edema of the intestinal wall. There was radiographic evidence of numerous phleboliths and calcification of vessels of both legs. Extensive pulmonary infarction occurred in 1940 followed by a loculated left pleural effusion which persisted for ten years and produced extensive fibrosis.

In 1945, steatorrhea was noted with two to four semi-formed bowel movements daily. Absorption studies included a normal glucose tolerance test (fasting level of 95 mg. per cent, maximum elevation 150 mg. per cent), impaired vitamin A absorption (serum vitamin A rose from an initial level of 51 μ g. per cent to 72 at four hours) and markedly impaired glycine absorption. These defects of absorption were attributed to edema of the small intestine secondary to hypoproteinemia. He was treated with a high-protein, low-fat, low-salt diet, liver extract and vitamin B₁₂ without improvement in hypoproteinemia and edema. He was under observation in the Nutrition Clinic for these features and was ultimately considered to be a case of idiopathic sprue resistant to conventional dietary and drug therapy. He was rehospitalized for institution of steroid therapy in 1951. Re-evaluation of his status revealed a chronically ill man with massive edema of both lower extremities simulating the picture of elephantiasis. There was swelling of the scrotum and slight pitting edema of the lower abdominal wall. Several areas of red, warm, slightly tender and indurated skin were present over the legs. The left chest was markedly contrasted with minimal expansion and scoliosis of the spine was present. Laboratory data revealed normal blood counts, normal minerals and electrolytes. The serum total proteins were 4.6 gm. per cent, with albumin 2.5 and globulin 2.1 gm. per cent. Roentgenologic study of the small intestinal showed thickening of mucosal folds, especially in the jejunum, interpreted as a "deficiency pattern". There was moderate generalized demineralization of the entire skeletal system and marked calcification of the arteries in the pelvis and the legs. Steatorrhea with fecal fat accounting for 30 to 40 per cent of the dry weight was present on repeated examinations despite the absence of diarrhea.

Corticotropin in daily doses of 60 to 100 mg. given for five weeks in the hospital failed to raise the serum proteins. Similarly, cortisone in daily doses of 80 to 100 mg., hydrocortisone 80 mg. and finally prednisone 40 mg. given in repeated trials between 1951 and 1956 produced no beneficial effects. The edema and hypoproteinemia persisted. Vitamin A absorption was impaired on repeated studies. The fasting serum vitamin A level averaged 40 μ g. per cent and rose to a maximum of 49. The serum carotene level was also low (15 to 24 μ g. per cent). The last roentgenologic study of the small bowel performed in 1956 revealed pseudodiverticulum of the jejunum, dilatation and increased secretion of the small bowel. Paper electrophoretic study of serum proteins showed marked depression of albumin and relative elevation of alpha-2 and beta globulin fractions (Table I, Case 9).

Comment: A 54 year old white man had intractable dependent edema due to hypoproteinemia for 27 years. The diagnosis of sprue was not made for 21 years. Steatorrhea, as well as mild diarrhea, malabsorption of protein and fats, and a slowly progressive deficiency pattern on roentgen examination of the small intestine was then noted. His course was further complicated by repeated episodes of phlebitis of the edematous legs and pulmonary infarction.

This case shows that chronic intractable edema and hypoproteinemia may be the outstanding clinical feature of the sprue syndrome even in the absence of severe manifestations of the disorder. This also illustrates the occurrence of selective dissociation of degrees of malabsorption of various substances and perhaps differences in the intensity of metabolic defects in sprue.

SERUM CHOLESTEROL, PHOSPHOLIPIDS AND TOTAL LIPIDS

Serum total and free cholesterol was determined by the Sperry-Schoenheimer method (12), phospholipids by Sperry's modification of the Fiske-SubbaRow method (13) and total lipids by the gravimetric method of Bloor (14). The determinations were performed on serum drawn in the fasting state.

Serum cholesterol determinations were performed in 76 patients with active sprue; phospholipids and total lipids, in 42 patients. Since serum cholesterol and phospholipid concentrations vary normally with age and sex (15) the levels of these lipids in sprue patients were separated accordingly (Figs. 1 and 2). For purposes of comparison, the average serum lipid concentrations in normal men and women were used. These were obtained from a survey performed previously in this laboratory from a 1200 person segment of the population of New York City (16).

Serum cholesterol concentration in the entire group of patients averaged 162 mg. per cent. Thirty-six (47.4 per cent) had serum cholesterol levels below 150;

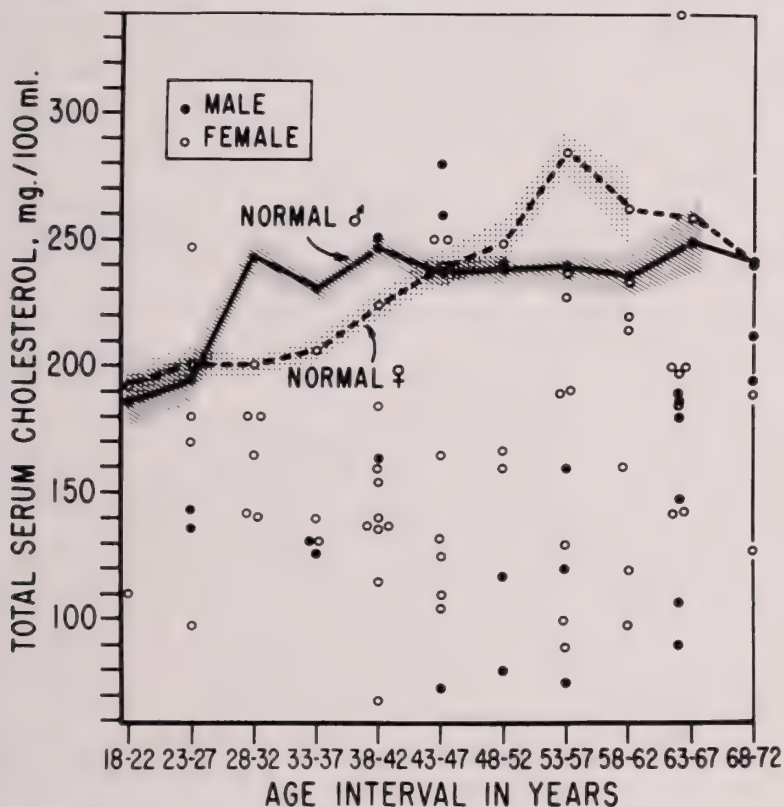


FIG. 1. Individual determinations of serum total cholesterol in 76 patients with idiopathic sprue separated according to age and sex. The curves represent the mean cholesterol levels obtained in healthy male and female controls at the various ages (16). The shaded areas represent one standard deviation from the mean.

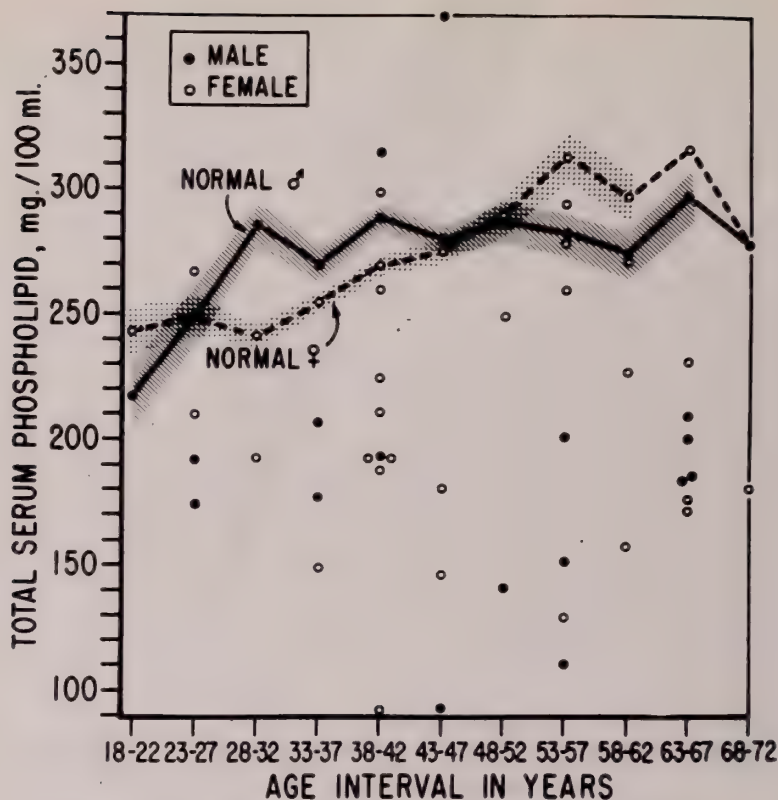


FIG. 2. Individual determinations of serum phospholipids in 42 patients with idiopathic sprue separated according to age and sex. The curves represent the mean phospholipid levels obtained in healthy male and female controls at the various ages (16). The shaded areas represent one standard deviation from the mean.

the lowest level was 68 mg. per cent. The low serum cholesterol levels were found mostly in patients who had been chronically ill for a long time or in acute crisis of active sprue. A graph of the individual determinations at various age levels, compared to the normal curve, showed that 88 per cent were lower than one standard deviation below the normal mean and 2.6 per cent were within one standard deviation (Fig. 1). In 9.4 per cent the values were greater than one standard deviation above the normal mean. These patients could be instances of idiopathic hypercholesteremia associated with sprue. There was no correlation between cholesterol levels, age and sex. The percentage of esterified cholesterol remained normal (75 per cent).

The average serum phospholipid concentration was 203 mg. per cent. The lowest level was 92 mg. per cent. Twenty-three patients (55 per cent) had levels below 200 mg. per cent. The lower levels of phospholipids were obtained in patients who had similar depression of cholesterol. Individual determinations are presented in Figure 2. Total lipid levels averaged 584 mg. per cent; 40.5 per cent of cases studied were below 500 mg. per cent. This serum lipid fraction was less depressed than either cholesterol or phospholipids.

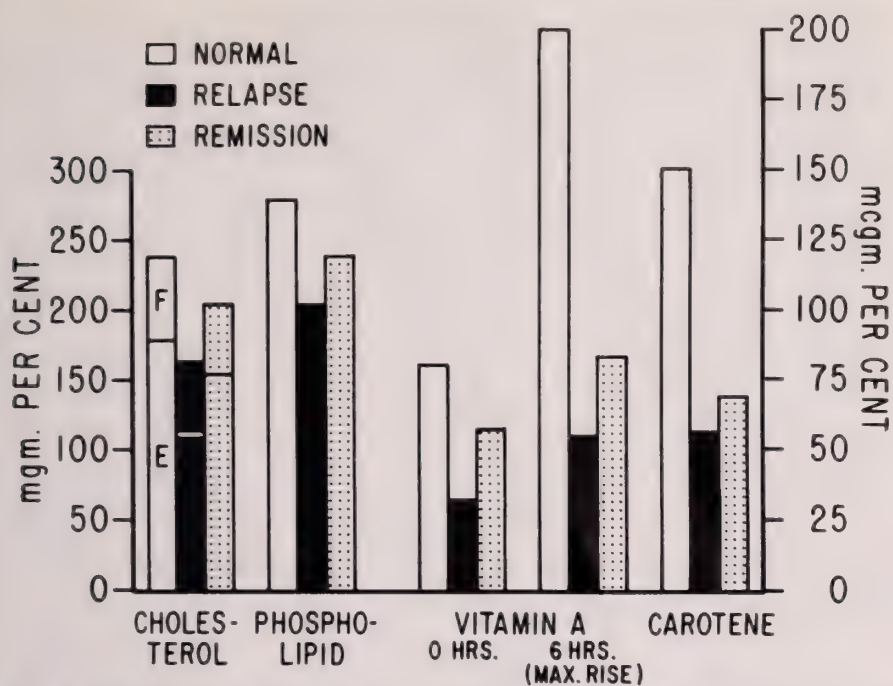


FIG. 3. Comparison of levels of serum cholesterol, phospholipids, "fasting" vitamin A, vitamin A six hours after oral administration of the vitamin, and carotene in patients with sprue in remission and relapse and in normal individuals. F = free cholesterol, E = esterified cholesterol.

In 29 patients serial study of serum lipid partition was performed during periods of therapy-induced clinical control. Levels of all lipid fractions were increased, but still remained below the healthy control levels (Fig. 3). Cholesterol levels were 203 mg. per cent (relapse, 162; control, 238). Phospholipids rose to 238 mg. per cent (relapse, 203; control, 278). Total lipids averaged 700 mg. per cent (relapse, 584; control, 700). Therefore, even in instances of full clinical control, some lipid levels remained depressed. This is illustrated by Figure 4 which depicts the clinical course and serum lipid levels of a typical patient with long-standing sprue who was followed during therapy with various adrenal cortical steroids.

Case 3

A 59 year old man with known idiopathic sprue for 27 years was hospitalized repeatedly for acute exacerbations of the disease as well as severe muscle and skin hemorrhages due to hypoprothrombinemia (17), possible subacute combined degeneration of posterior and lateral columns of the spinal cord (18), and marked generalized osteoporosis (osteomalacia) with fatigue fracture of the femoral neck (19). Because of the resistance to conventional dietary and anti-anemic therapy over a nine-year period, steroid therapy was instituted and resulted in clinical control during the last 5½ years. The maintenance dose was 12.5 mg. for cortisone and 15 mg. for hydrocortisone free alcohol. At present he is controlled on 10 mg. of prednisolone daily. During this period there was a decrease in number of bowel movements and gain in weight, with return to full activity, as the various steroids were ad-

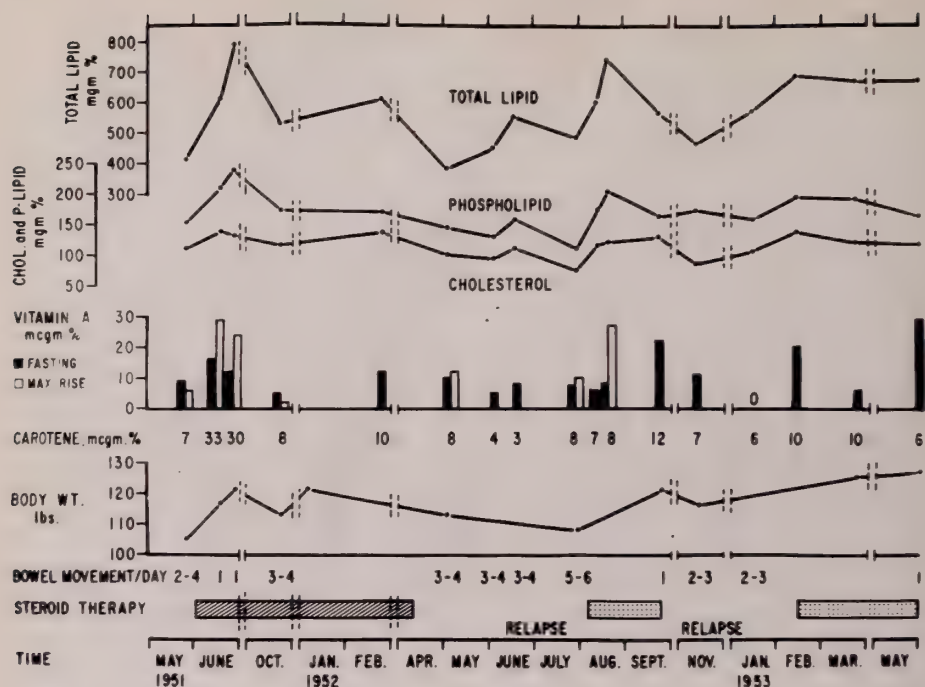


FIG. 4. Case 3, a 59-year old man with long-standing idiopathic sprue whose symptoms were controlled by treatment with a variety of steroids over a period of three years, two of which are presented in this graph. Attempts to withdraw these agents resulted in relapses. Variations in serum lipid fractions are correlated to changes in absorption of vitamin A and levels of serum carotene and to the clinical status of the patient. Response to therapy is indicated by gain in body weight and diminution in number of bowel movements daily. The three courses of steroid therapy consisted of cortisone (June 1951 to April 1952), hydrocortisone (August to September 1952) and hydrocortisone (February to May 1953).

ministered. However, serum lipid, vitamin A and carotene levels remained persistently low. Attempts to withdraw steroids resulted on three occasions in clinical relapse.

While there was an increase in concentration of serum lipids in association with good response to therapy in this and other patients, these levels were still markedly depressed. It is known that there is an increase in serum lipid levels under the influence of large doses of adrenal cortical steroids (20). Sprue patients under therapy receive a minimal maintenance dose of steroids which is therefore not the factor responsible for the lipid elevations. Rather, these may be a reflection of increased absorption, gain in weight and general clinical improvement as a result of therapy.

VITAMIN A TOLERANCE TEST AND SERUM CAROTENE LEVELS

Vitamin A absorption tests were performed following the oral administration of 180,000 i.u. of vitamin A in oil (3 ml. of Oleum Percomorpheum, Mead-Johnson). Serum vitamin A levels were analyzed by the micromethod of Bessey, et al. (21). The fasting levels of vitamin A obtained by this method ranged from 60 to 100 μ g. per cent in healthy persons (22). In ten normal persons determina-

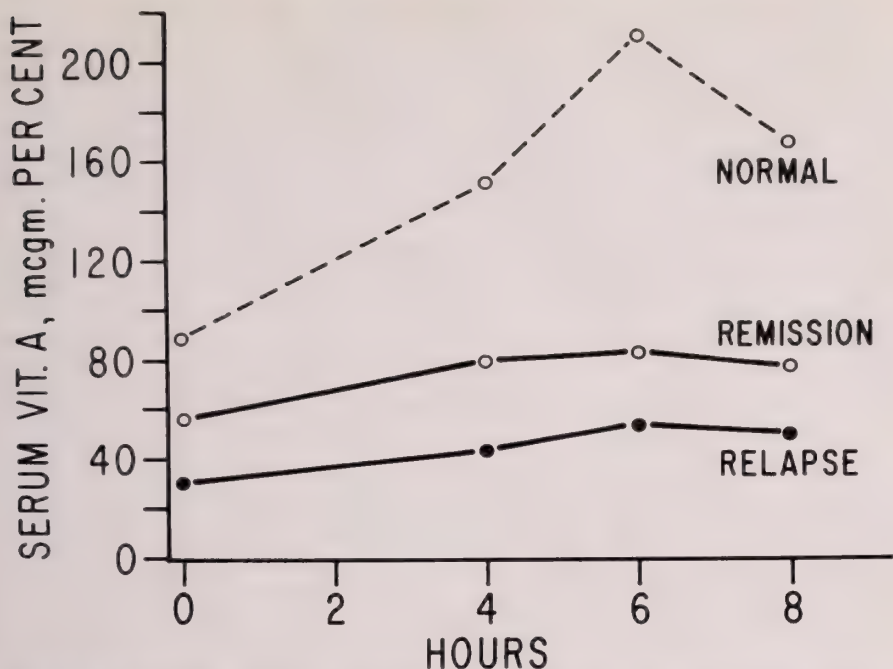


FIG. 5. The average vitamin A tolerance curve obtained in 54 patients with sprue in relapse compared with 29 sprue patients under clinical control. The normal absorption curve was the average of values obtained in ten healthy individuals.

tions were performed in the fasting state and four, six and eight hours after the vitamin A administration. The average values at fasting, four, six and eight hours were 87.0, 151.2, 210.1, and 167.9 $\mu\text{g. per cent}$, respectively (Fig. 5). The maximum rise occurred six hours after the ingestion of vitamin A and amounted to 123.1 $\mu\text{g. per cent}$ over the fasting level. The occurrence of peak levels five to six hours after the test dose has been noted by others (23-25).

Of the group of 94 patients with idiopathic sprue in relapse, vitamin A absorption tests were done in 54. The serum vitamin A concentration in the fasting state averaged 31.3 $\mu\text{g. per cent}$ (range 0 to 124). In 91 per cent the level was below 60 $\mu\text{g. per cent}$. In four patients low normal values were obtained. One patient had a moderately high fasting level (124 $\mu\text{g. per cent}$).

The absorption of vitamin A in the 54 patients with idiopathic sprue was considerably impaired (Fig. 5). The average values four, six and eight hours after the test dose were 43.2, 53.5 and 49.2 $\mu\text{g. per cent}$, respectively. The maximum rise occurred at six hours and amounted to an increase of 22.2 $\mu\text{g.}$ above the average fasting level. Eight patients (14.8 per cent) showed no absorption of vitamin A during the eight hour test period. In these patients the serum vitamin A after vitamin A intake was either unchanged or lower than the initial level. Fifteen patients (27.8 per cent) had a maximum rise of less than 10 $\mu\text{g. per cent}$ above the fasting level; 12 (21.8 per cent), less than 20 $\mu\text{g. per cent}$; 13 (23.6 per cent), less than 60 $\mu\text{g. per cent}$ and 7 (12.8 per cent), less than 120

$\mu\text{g. per cent.}$ In none of the patients did the maximum rise of serum vitamin A exceed $120 \mu\text{g.}$

In six patients, the maximum rise of serum vitamin A was delayed and occurred eight hours after the oral administration of the vitamin. These patients usually showed negligible absorption of vitamin A in the first four to six hours. The average values of serum vitamin A in this group of patients were 39.3, 42.3, 47.3 and $61 \mu\text{g. per cent}$ at fasting, four, six and eight hours, respectively.

In 29 patients, repeated vitamin A tolerance tests were performed during the stages of relapse and remission. The fasting serum vitamin A level was found to be higher during remission in all patients ($57.0 \mu\text{g. per cent}$). During remission the average levels four, six and eight hours after vitamin A administration were 79.0, 82.0 and $77.3 \mu\text{g. per cent}$, respectively. The mean maximum rise of serum vitamin A six hours after the oral test dose was $25.0 \mu\text{g. per cent}$. As shown in Figure 6, the entire absorption curve during remission was on a higher level than during relapse; but the rate of absorption was probably not altered.

The serum carotene level averaged $56.3 \mu\text{g. per cent}$ in the same group of 54 patients in relapse. This level was considerably lower than values seen in normal persons (100 to $200 \mu\text{g. per cent}$). In two patients, serum carotene was undeterminable; in 25 (45.5 per cent), the level was below $20 \mu\text{g. per cent}$ (Fig. 6). In only five of the 55 patients (9.1 per cent) was the serum carotene level

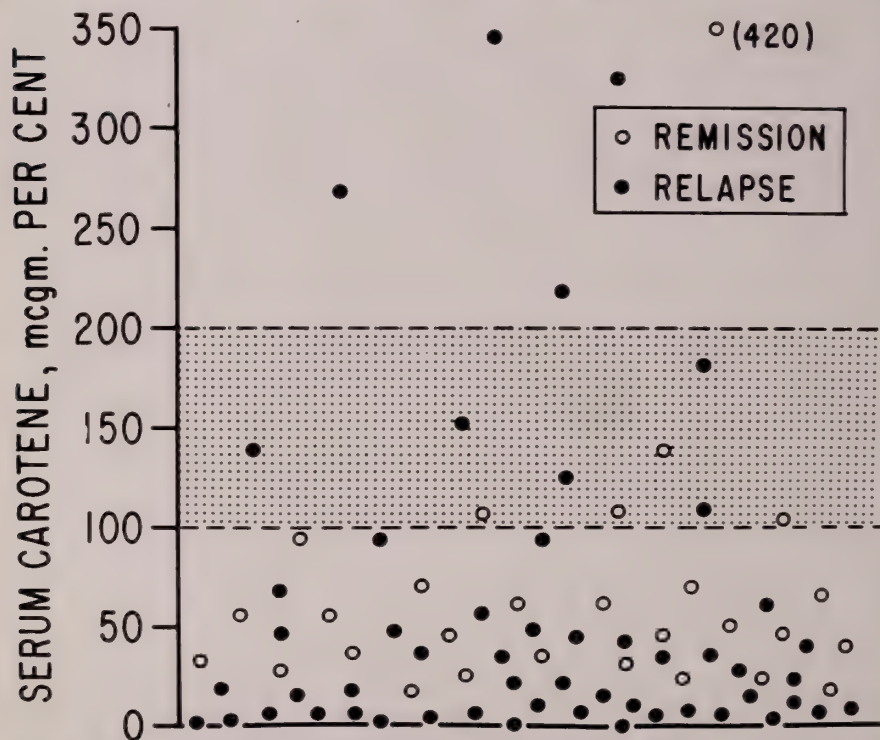


FIG. 6. Individual serum carotene levels in 54 patients with idiopathic sprue in relapse compared with 28 sprue patients under clinical control. The shaded area represents the range of normal serum carotene concentration.

within normal limits during relapse. All five were clinically milder instances of sprue. Their average fasting vitamin A level was also normal (69 $\mu\text{g.}$ per cent). The normal serum carotene level in these patients may be interpreted as indicative of adequate carotene absorption. The latter was associated with a slightly impaired vitamin A absorption. Five other patients (9.1 per cent) had high serum carotene levels of 218, 268, 325, 346, and 347 $\mu\text{g.}$ per cent, respectively. These five patients were also milder cases of sprue. Their serum vitamin A levels averaged 47.4 $\mu\text{g.}$ per cent in the fasting state and rose to an average of 110.4 $\mu\text{g.}$ per cent after the administration of vitamin A. This suggests that the presence of carotenemia may coincide with apparently normal vitamin A absorption in patients with sprue.

In 28 patients the serum carotene concentration was determined during remission. The average value for the group was 70.7 $\mu\text{g.}$ per cent. The majority, 15 patients or 56.5 per cent, showed levels between 20 and 60 $\mu\text{g.}$ per cent. In three patients, the serum levels became normal during remission, ranging from 104 to 117 $\mu\text{g.}$ per cent. One patient who had a normal value during relapse became hypercarotenemic during remission (420 $\mu\text{g.}$ per cent). This patient had a serum cholesterol level of over 300 mg. per cent on repeated examinations and is probably a member of a family with idiopathic hypercholesteremia. Thus, one may expect that these patients would have normal serum lipid, vitamin A and carotene levels with active sprue in relapse which then return to their originally high values during remission.

DISCUSSION

Hypoproteinemia and especially hypoalbuminemia is a constant feature of the full-blown sprue syndrome and is frequently associated with evidences of water retention such as edema, and at times ascites (4). Low levels of both serum albumin and globulin have been observed in large series of sprue patients; edema occurred when the total protein fell below 5 gm. per cent (6).

In the present group there was good correlation between levels of serum proteins (albumin) and the appearance of edema. On the other hand, Cooke, Peeney and Hawkins could find no correlation between edema and the level of the serum proteins in reviewing 100 patients with idiopathic steatorrhea (5). In two of their patients edema coincided with severe anemia, a finding which was not prominent among our patients. Comparison of the two series (The Mount Sinai Hospital in New York and the General Hospital in Birmingham, England) reveals a higher incidence of hypoproteinemia (19 per cent versus 7 per cent) and particularly of hypoalbuminemia (52 per cent versus 40 per cent) in our series. This may be a reflection of the more severe character of the sprue syndrome encountered in our group of patients.

None of the patients examined were found to exhibit the syndrome of agammaglobulinemia, recurrent infections and sprue, as has been reported (9). No characteristic pattern of alteration in serum globulins could be established by paper electrophoresis in the present group of patients although a variety of changes were observed.

The findings of depressed levels of serum lipids in patients with active sprue

are in accordance with previous observations on this subject (1-3, 5). Keele demonstrated that fat absorption may remain below normal during remissions induced by liver extract (26). It is of interest that the serum lipid levels remained depressed in some patients even under good clinical control. This suggests that malabsorption is probably not the sole responsible factor and implies other as yet undetermined metabolic defects concerning lipid synthesis (3).

Malabsorption of fat-soluble vitamins is one of the conspicuous features of the idiopathic sprue syndrome. The absorption of vitamin A and carotene has been used by many investigators as a diagnostic test for this disorder (22, 24, 27, 28). Similarly, impaired absorption of vitamin E is probably responsible for the low serum levels of this vitamin in sprue (29).

In patients in full clinical remission serum vitamin A levels are often higher than in patients in relapse. The improved absorption can be detected only occasionally during the short eight-hour period of the absorption tests. The "tolerance curves" usually remain flat. This indicates that increased absorption of vitamin A over a prolonged period of time must occur to produce the increment in serum vitamin A. Correlation of fat balance studies with vitamin A tolerance test showed that the vitamin A tolerance curve became flat when fat absorption fell below 75 per cent (24).

Pretreating sprue patients with large doses of vitamin A for several days prior to performing a vitamin A tolerance test resulted in elevation of the serum levels of the vitamin but the "tolerance curves" remained flat indicating malabsorption (27, 30). This observation suggests that absorption of vitamin A is not directly correlated with the "fasting" serum level.

While patients presenting the classical clinical symptoms and signs of idiopathic sprue can be easily recognized, the clinical variants of incomplete sprue are usually diagnostic problems (7, 31). Hypoproteinemia, probably caused by malabsorption of protein as well as impaired synthesis, can be a presenting symptom. Case 1 illustrates that severe hypoproteinemia and edema can persist for years before appearance of the more classical and severe symptoms of diarrhea, tetany and hypocalcemia. Case 2 shows that massive intractable leg edema and repeated episodes of erysipelas, cellulitis and phlebitis may be associated with a mild form of the disorder.

In other patients, clinical features of malabsorption of lipids and fat-soluble vitamins predominate. Many patients present hemorrhagic manifestations resulting from malabsorption of vitamin K as the chief clinical feature of idiopathic sprue (17). Steatorrhea may be overlooked in the absence of diarrhea. Case 3 illustrates persistent low levels of serum cholesterol, phospho-lipids, total lipids, vitamin A and carotene even under full clinical control in a patient with long-standing classical sprue observed over a period of many years. The serum vitamin A and carotene diminished to undeterminable levels during relapse. Hemorrhagic phenomena and osteomalacia in this patient were clinical manifestations of concomitant deficiencies in vitamins K and D.

Thus, pronounced defects in the serum levels and in the turnover of proteins and lipids represent an essential part of the metabolic derangement observed in

the malabsorption syndrome. Other facets of this metabolic disturbance are alterations in the metabolism of water, iron, calcium, phosphorus, sodium and potassium. Additional discussions of these aspects are presented in other parts of the symposium (17, 32, 33).

SUMMARY

Patients with idiopathic sprue may present profound alteration of serum proteins and lipids as outstanding features of the disorder.

Study of serum total proteins, albumin and globulin in 67 patients with active sprue revealed low values which were correlated in 16 patients with the presence of edema. In 20 patients, sera were further fractionated by paper electrophoresis. Non-specific alterations in serum globulins were generally noted. In two patients (Cases 1 and 2), the clinical course of the sprue syndrome was characterized by protracted edema and hypoproteinemia as early manifestations of the disorder.

Serum cholesterol concentration studied in 76 patients and phospholipids and total lipid determined in 42 patients with active sprue yielded low levels. In 29 patients under clinical control, levels of lipid fractions increased but still remained low in many instances. This is illustrated by Case 3 who showed persistently depressed levels of all lipid fractions, despite good clinical control and evidence of improved absorption.

Vitamin A and carotene levels were low in 54 patients with active sprue and absorption of the vitamin was considerably impaired. While in 29 patients under good clinical control serum levels of vitamin A and carotene were higher, the absorption curves of vitamin A remained flat.

These observations suggest that disturbances in the metabolism of proteins and lipids are not always related to malabsorption *per se*.

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WATER AND ELECTROLYTE UPSETS IN THE STEATORRHEA SYNDROME

W. TREVOR COOKE, M.D., F.R.C.P.

It has become increasingly evident that any disorder which is associated with diarrhea may manifest the clinical signs of electrolyte depletion; it has not been as widely recognised that conditions affecting the intestine in which diarrhea is not necessarily a prominent feature also provide similar upsets. The normal subject passes 100–200 ml. of water per day in his stools and 2–5 mEq. Na and 10–15 mEq. K. Increase in the amount of water in the stools, as for example in any patient with diarrhea, is associated with an increase in the excretion of sodium, so that there appears to be a direct relation between the two. The amounts of sodium that may be found in severe diarrheas may be as much as 200–250 mEq. per day. In patients suffering from non-tropical sprue it has been found that there is an increased fecal excretion of potassium, even in formed stools when the water content is less than 250 ml. per day. In such instances, the daily excretion of potassium is around 25 mEq. though on occasions as much as 60 mEq. may be found. With an increase of the fluid content, the amount of potassium stays relatively unchanged until large quantities of water are being passed. The potassium excreted then increases to help maintain the isotonicity of the colonic contents. Even so, the amounts of potassium in the stools do not usually exceed 100 mEq. (1) (Figure 1). The reasons for this increased excretion of potassium in the stools of patients with steatorrhea are not readily apparent. It appears to be entirely endogenous in origin for the administration of large amounts of potassium by mouth does not lead to any significant increase in the feces and of a dose of K^{42} given intravenously, 20 per cent is excreted in the feces and 80 per cent in the urine.

In addition to the upsets in the fecal excretion of water and electrolytes, many patients with steatorrhea show upsets in urinary excretion of water, as evidenced by a marked nocturnal polyuria. This manifestation appears when the patients are in relapse and usually clears up completely when the patients are well. It can be the most troublesome symptom, causing the patient to rise 4 or 5 times per night to pass urine. Even on a daily intake of 12–1400 ml., urine volumes as high as 4 ml. per minute may be passed between 12 midnight and 1 a.m. There is no evidence that this is caused by an electrolyte diuresis, but rather it appears to be an inversion of the normal diurnal rhythm, whatever the physiological cause for this may be. Wollaeger and Scribner drew attention to the poor diuresis that follows oral ingestion of water in patients with the severe form of the disorder (2). They suggested that the nocturnal diuresis was related to the retention of large volumes of water in the small intestine during the abnormally prolonged period necessary for digestion and absorption of food. They demonstrated clearly that the diuresis could not be accounted for by the difference in

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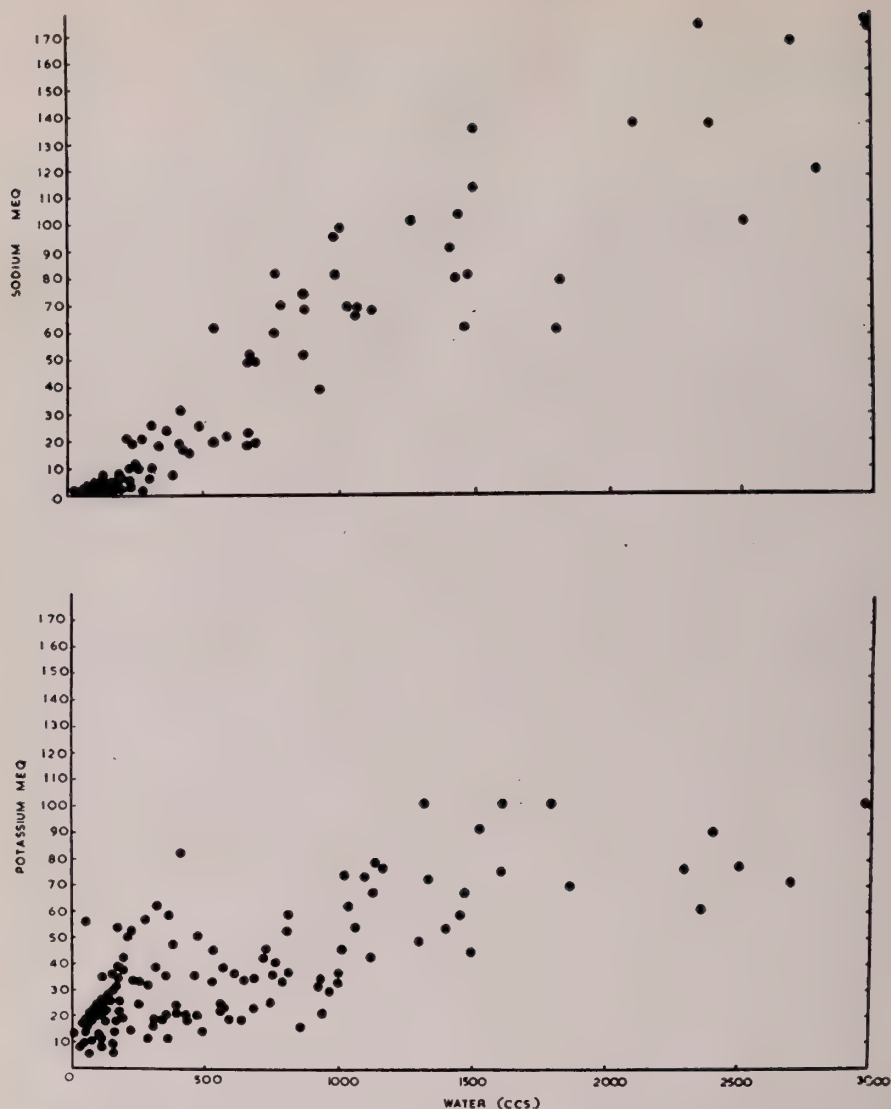


FIG. 1. Twenty-four hour fecal excretion of Na and K plotted against that of water in patients with steatorrhea.

posture during day and night or by renal disease. They also pointed out that the time of diuresis was influenced by the time of taking food and also that increasing the fluid intake increased the volume of the night urine rather than the daytime urine, though beyond a certain increase in intake, no further increase in nocturnal diuresis was effected and the daytime urine increased (Figure 2). One point of clinical interest emerging from these observations was that some patients with steatorrhea can give false positive results in Kepler's water test for Addison's disease. This point is especially important when it is remembered

that many patients with steatorrhea are pigmented (a few may also have pigment in their mouths) and have low blood pressures, asthenia and often disturbed serum electrolytes. Wollaeger and Scribner focussed attention on the possible delayed absorption of water from the intestine. With the use of heavy water, Reitemeier, Higgins, Lee and Scholar have demonstrated that there is indeed a lower rate of absorption of water which rights itself as the patient improves (3). It is of interest that the rate was not speeded up by the administration of cortisone even though the patient's general condition approached normality with this therapy. French and Newsholme found a somewhat comparable delay in the absorption of Na^{24} (4).

Taylor has extended the initial observations of Wollaeger and Scribner (5-7). He agreed with their hypothesis of a delay in water absorption and pointed out the great delay in excreting water following the oral administration of a liter of water. He found a significant positive correlation between the degree of this delay and the degree of impairment of fat absorption. He did, however, find a

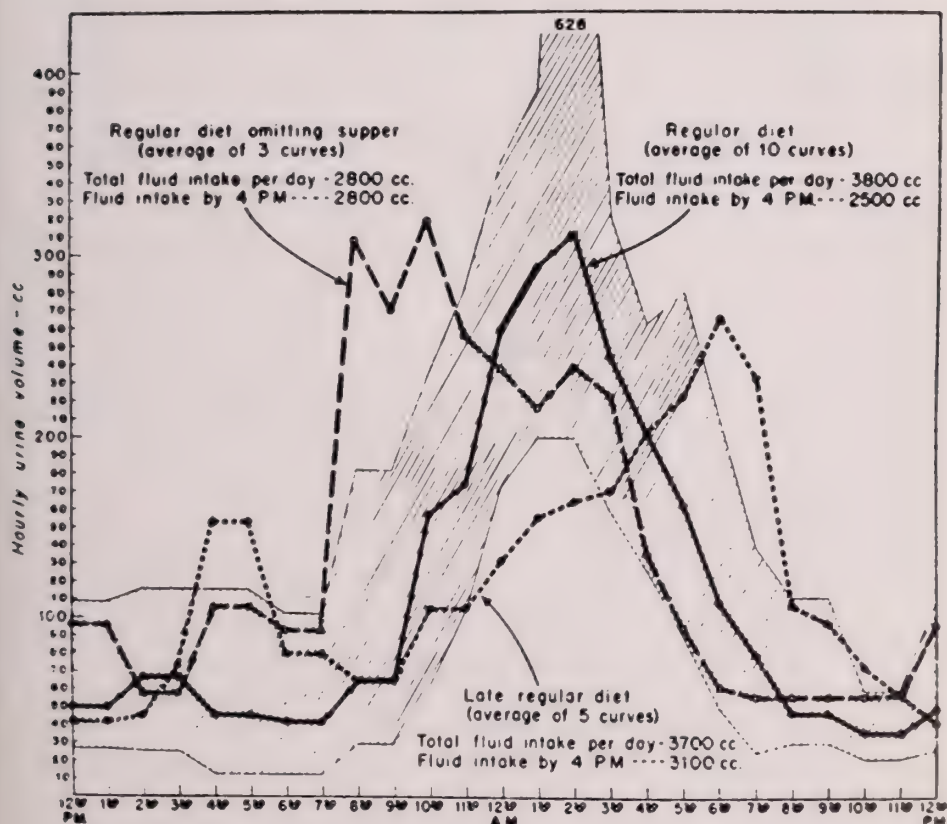


FIG. 2. Hourly volumes of urine of a patient with non-tropical sprue taking (1) the regular standard diet, (2) the same diet with meals delayed four hours and time of fluid ingestion kept approximately the same and (3) the same diet with omission of all food at 3:30 p.m. (Reprinted from *Gastroenterology*, 19: 224, 1951 (2)).

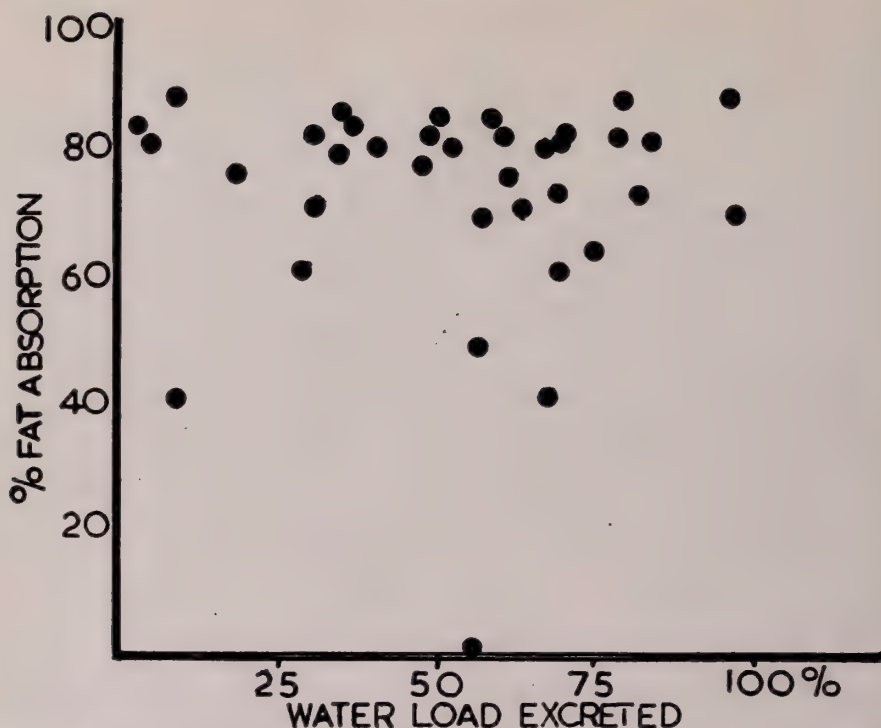


FIG. 3. Severity of steatorrhea, for convenience expressed as per cent absorption, plotted against a defect in water diuresis, expressed as the per cent excreted of the water load ingested.

similar delay in patients with untreated pernicious anemia which almost disappeared when treated, though not completely returning to normal. In pernicious anemia he believed that there was initially a delay in water absorption but a renal factor might also be implicated, preventing the complete return to normal. Observations in other conditions may provide a clue on the mechanism of the delayed diuresis in steatorrhea. In a series of 35 patients with steatorrhea, Flear and Cooke were unable to find any correlation between the degree of delayed diuresis and the defect in fat absorption (8) (Figure 3). Nor could any correlation be found between the diuretic response and the serum proteins or the hemoglobin. Little or no modification of the response was noted with hydrocortisone. The Na^{24} and K^{42} spaces were determined simultaneously in 11 patients, but again no correlation could be found between the delayed diuresis and the exchangeable masses of Na and K (Table I). Similar delays in diuresis were noted in patients with cirrhosis of the liver, congestive cardiac failure, ulcerative colitis and severe hypokalemia, while completely normal responses were obtained in two patients with severe hypoproteinuria. The similarity in response in these several conditions raises the question as to whether the apparent delay in water and sodium absorption is the complete explanation of this upset in water excretion. In one patient, the nocturnal diuresis continued unchanged during the

administration of fluid continuously for seven days by a gastric drip, suggesting that there may well be some more fundamental defect causing this phenomenon. This suggestion was supported by observations on patients with regional ileitis with steatorrhea and apparently normal radiological patterns of the intestinal mucosa in the jejunum and upper half of the ileum. In none of these cases was the fecal excretion of water more than 400 ml. per day, but in all there was the same delay in diuresis and increased nocturnal excretion of water.

The possibility of renal changes playing some part cannot entirely be ruled out for the occurrence of tubular nephropathy has been reported by Ohler (9) and has been found in a number of our patients at post-mortem, though in none on whom the diuresis tests had been carried out (Figure 4). Whether the simple mechanical explanation of delayed absorption will prove the correct explanation for this upset in water excretion remains to be seen; but vitamin B₁₂ deficiency, folic acid deficiency, chronic potassium depletion, liver dysfunction or even a functional disturbance of the brain stem may all play their part in bringing about this disturbance.

While the dangers of marked electrolyte depletion during any severe diarrhea is now well recognised, the development of severe deficits following a prolonged slight negative daily balance in patients with little or no diarrhea has not re-

TABLE I

Values for exchangeable potassium and sodium in patients with steatorrhea determined simultaneously with the water diuresis test

	Age	K _e	K _e /kg.	K _e /cm.	Na _e	Na _e /kg.	Na _e /cm.	3 hr. % Excretion‡
<i>Male</i>								
Mean normal*		3418	46.8	19.6	3029	41.6	17.3	
Coeff. var.		12.4	11.7	10.7	12.7	14.4	11.5	
Patients†	47	50.0	75.4	53.7	67.2	101.3	72.9	73
	58	58.9	72.3	61.7	86.6	106	91.3	30
	47	71.9	84.0	69.4	79.3	92.5	76.9	44
	33	57.2	83.6	60.3	94.8	139.2	100.6	62
	53	75.6	92.7	72.1	74.3	91.1	71.1	66
	25	70.4	105.1	75.5	63.3	95.2	68.2	94
	57	65.0	81.7	66.8	113.2	141.9	116.6	3
<i>Female</i>								
Mean normal*		2449	41.2	14.9	2328	40.2	13.8	
Coeff. var.		10.9	9.2	9.8	11.9	8.3	9.5	
Patients†	53	71.0	80.6	74.1	80.3	89.1	86.0	66
	49	58.0	91.5	65.8	119.6	183.8	139.2	58
	49	62.3	93.2	71.1	84.2	122.6	97.9	49
	26	66.1	91.0	69.1	93.2	124.8	100	60

* The values for normal have been computed from the literature and are expressed in absolute amounts (mEq.).

† The results in the 11 patients with steatorrhea are expressed as per cent of the mean normal values.

‡ The 3 hour excretion represents the per cent of the water load excreted during that time in the Kepler water test.

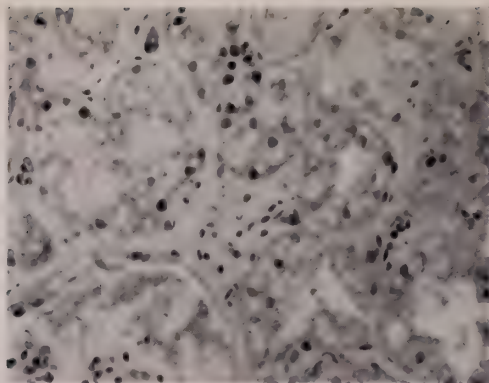


FIG. 4. A photomicrograph of kidney showing tubular nephropathy associated with potassium deficiency in a 53-year old man who died with idiopathic steatorrhea. This patient had become depleted of electrolytes on a number of occasions during the 6 years he was under observation and, although no controlled observations had been made on water excretion, he had marked nocturnal diuresis during his periods of ill health.

ceived as much attention as it deserves. In order to give quantitative backing to this belief, Blainey, Cooke, Quinton and Scott studied the available stores of potassium with isotopes in 12 patients with idiopathic steatorrhea (10). They found that the values for the males and females were only 63 and 58 per cent of the mean normal values computed from values in the literature. These initial observations were considerably extended by Flear, Quinton, Cawley and Cooke on a further 23 patients (11). A number of different conditions were studied, though the majority of patients were suffering from non-tropical sprue; none had any evidence of marked dehydration. In 21 of the 23 patients studied by this technique the exchangeable values for potassium were significantly lowered, the other two being 81 and 82 per cent of the mean normal levels and in good health at the time of the observations. The results in the other 21 patients, however, might have meant only that the patients had all lost weight, for when the results were standardized to a unit of body weight, 16 were not significantly different from normal though only five had values equal to or greater than the mean normal. The remaining five patients had evidence of intracellular depletion of potassium. By analyzing the data with exchangeable potassium referred to a unit of body height, evidence could be obtained that the lower total exchangeable potassium in 16 of the 23 patients was due to intracellular depletion of potassium and loss of lean tissue combined. The exchangeable K (K_e) for the 34 observations in 23 patients was 58.7 per cent of the mean normal (range 15.6–82.0), expressed as mEq. per kg.—77.8 per cent (range 27.3–105.7), expressed as mEq. per cm.—63.7 per cent (range 16–86.7). A similar analytical approach to the data of Blainey et al. suggested that, of the 12 patients, in 9 the lowered K_e was due to loss of intracellular potassium and lean tissue and in the remaining three, there was loss of intracellular potassium and body fat with or without lean tissue loss in addition.

In 20 of these patients, the exchangeable stores of sodium were estimated

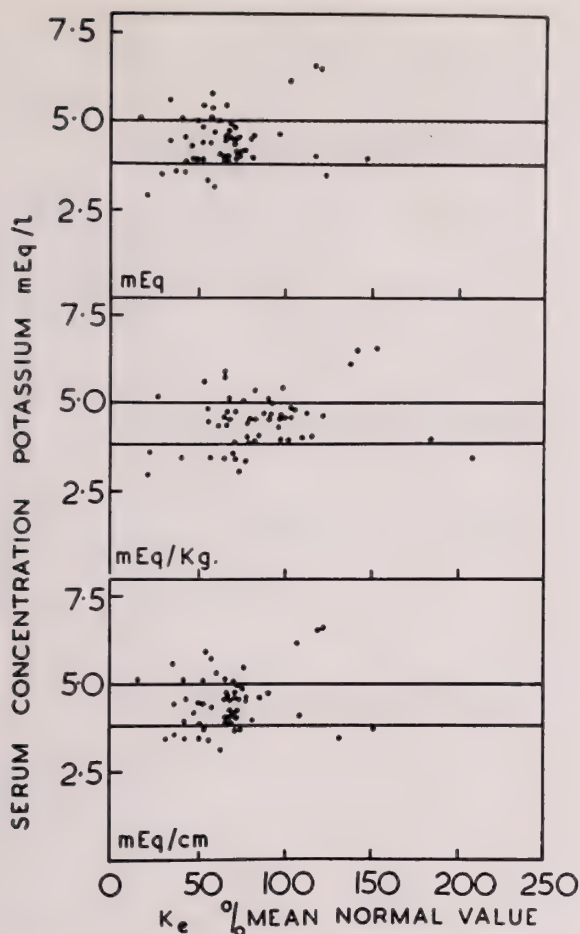


FIG. 5. Fifty-six observations on 38 patients with steatorrhea, showing absence of relationship between serum K and K_e (expressed as percentage of mean normal values.) Shaded areas represent the normal range (80 per cent confidence, Wootton, I. D. P., King, E. J., *Lancet*, *i.e.*, 470, 1953.)

simultaneously with those of potassium. There was little evidence of any significant deviation from the mean normal in these patients and in 12 the results fell within normal ranges. For the 20 patients, exchangeable (N_{ae}) was 103.3 per cent of mean normal (range 78.0–139.4), expressed as mEq./kg.—110.7 per cent (range 72.6–141.9), as mEq./cm.—92.5 per cent (range 68.2–139.2). Since none of these patients was suffering from severe diarrhea or had evidence of gross dehydration at the time of study, these results are not surprising.

As has been pointed out by Moore et al. serum levels of potassium are not a reliable guide to the stores of exchangeable potassium (12). In Figure 5, the findings in a series of 38 patients are depicted. It can readily be seen that the serum values within normal ranges have little significance. It is important to realize, therefore, that many patients with steatorrhea have deficient stores of

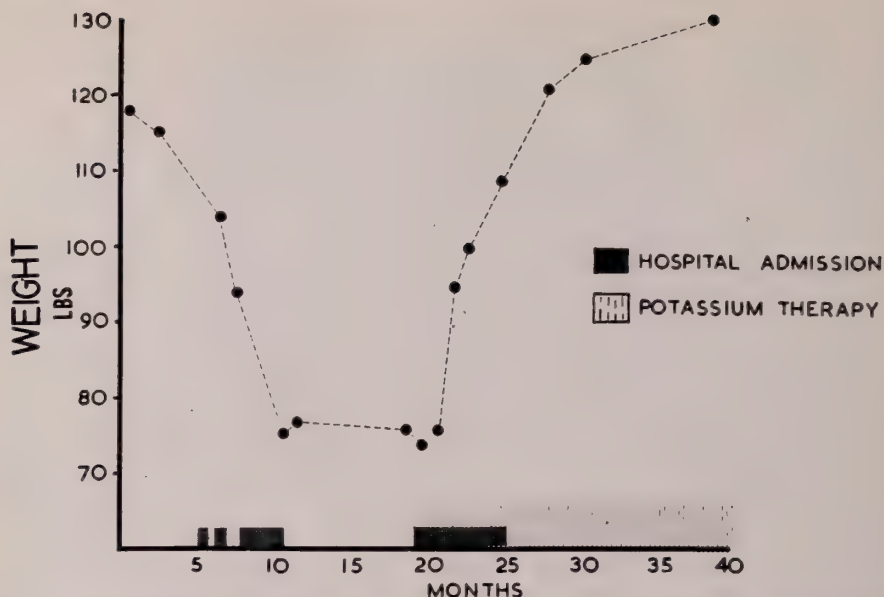


FIG. 6. The effect on weight of addition of potassium therapy in a 56-year old woman with regional ileitis and a bypassed loop.

available potassium and that in some this deficiency will be of severe degree. In view of this, it is still more important to recognize the symptoms which may be produced, in some part at least, by potassium deficiency.

Weight loss. Weight loss is one of the commonest symptoms in the malabsorption syndrome. In a series of 100 patients with non-tropical sprue Cooke, Peeney and Hawkins found that the average weight loss at the time the patients were first seen was 28 pounds (13). There are of course many factors bringing this about, but, unless there are adequate stores of potassium, the patient will find it difficult to regain his normal weight. In a few patients, it can be demonstrated that extra supplements of potassium are all that is necessary to allow return to normal weight. A particularly striking, though probably exceptional, example is depicted in Figure 6.

This woman was first seen in 1945, aged 52, on account of diarrhea and progressive loss of weight during the previous five years. In 1939 an ileo-colectomy without exclusion had been performed for an obstructive lesion in the right iliac fossa, thought to be regional ileitis. On admission, she weighed 73 lb. Her blood count was 1.9 million red cells and hemoglobin 8.0 gm., MCV 150 cu. μ . She was excreting over 40 gm. of fat daily. Treatment with a crude liver extract caused her blood to revert slowly to normal values. At the end of 12 months the red cell count was 4.92 million, hemoglobin 14.8 gm., MCV 84 cu. μ . Her weight increased to 140 lb. Despite persistence with regular liver therapy and admission to the hospital on two occasions her weight gradually fell over the next four years to 73 lb. The addition of folic acid had restored her blood count to normal while calciferol, nicotinic acid and riboflavine controlled her cramps and glossitis. In 1950 she was admitted mentally confused and greatly wasted. Her serum potassium was found to be 3.0 mEq. per liter. Dehydration was corrected; therapy with folic acid, liver extract and B vitamins was continued and intensive potassium therapy initiated. Her weight increased as depicted in

Figure 6. Her blood count was maintained at normal levels; her loose stools continued 5-6 times daily and she was able to run her home. In 1955, following a severe attack of diarrhea, she had a severe prolapse of her rectum. X-ray investigation confirmed the provisional diagnosis that a large portion of the small intestine had been bypassed. An operation was, therefore, performed which revealed an anastomosis between the jejunum, one foot below the duodeno-jejunal flexure, and the transverse colon and normal continuity was restored. The remainder of the small intestine was normal except for a number of scars involving the wall of the mid-portion of the ileum. Following operation, her diarrhea ceased, she passed normal colored, formed motions 1-2 a day. Her fat excretion, which was 10-15 gm. per day prior to operation, fell to 6 gm. per day 10 days after operation. No further therapy has been given. Her weight is now constant 18 months after operation at 142 lb. and her blood count normal in all respects.

Intestinal distension and ileus. Streeten and his colleagues have demonstrated the importance of the normal electrolyte content of the intestinal cell for the maintenance of the normal tone of the intestinal muscle (14). With increasing depletion of intracellular potassium, ileus eventually becomes manifest. The possible importance of this work in the steatorrhea syndrome is self evident. It may well provide the explanation for the increase of the intestinal lumen, a characteristic finding on radiological examination of the small intestine in idiopathic steatorrhea. In minor degrees of depletion, abdominal distension is common. Such symptoms have usually been attributed to intestinal fermentation with excessive gas formation, but the relief obtained with potassium therapy suggests that potassium deficiency is probably a primary cause.

More dramatic manifestations are those of volvulus and intestinal obstruction. Adlersberg and Glazer have drawn attention to this group of patients and the importance of early recognition to prevent actual gangrene of the gut (15). In many patients with steatorrhea, the colon appears to be excessively long, thus it is not surprising to meet, in such patients during periods of abdominal distension, attacks of abdominal pain, often relieved by the adoption of the knee-elbow position. The distension of any hollow tube, e.g. a bicycle tube, within a semi-rigid container is obviously liable to cause kinking and obstruction to the free passage of the contents of that tube. Clinically, such kinking may simulate acute intestinal obstruction sufficiently closely to mislead the most experienced. Adlersberg has described the volvulus that may occur. Recognised early, vigorous restoration of fluids and electrolytes will relieve the condition, though should the attack be of such duration as to raise doubt on the possible viability of the bowel, laparotomy may be necessary also.

Another confusing picture that may appear independently of the attacks of abdominal pain is recurrent vomiting which has been the presenting symptom in a few patients, suggesting either pyloric stenosis or gastric neoplasm. Such vomiting is due to partial volvulus of the stomach associated with the general intestinal atony, the dilated colon displacing the stomach and so bringing about the volvulus.

Neuropathy and mental disorder. Neuropathy is not uncommonly encountered in the malabsorption syndrome, showing itself in a variety of ways—peripheral neuritis, cord degeneration and, occasionally, cerebral or cerebellar degeneration.

In a study of 26 such cases, no evidence of a primary potassium deficiency could be found, though in view of Biermond and Polkadaniels' observations in periodic paralysis, chronic potassium deficiency might play some part in the initiation of organic nervous disease (16). Severe hypokalemia will on occasions be associated with a peripheral neuritis which rapidly clears up with the relief of the hypokalemia. Similarly, severe psychoses occasionally occur and, with the underlying cause not being recognized, may result in the patient being committed to a mental hospital (17).

Tetany. Tetany has long been recognised as one of the features of the severe sprue syndrome. It is, however, rare to find a patient with troublesome recurrent tetany who does not also have fairly severe depletion of potassium. The recognition of this association has enabled us successfully to relieve patients who had long resisted conventional therapy with extra calcium and vitamin D and to restore normal levels of calcium in the serum. This was strikingly demonstrated in one patient with such symptoms in whom complete relief was obtained with intensive potassium therapy and rehydration but without any added calcium or vitamin therapy. The demonstration of increased urinary excretion of phosphate during hypokalemia by Mahler and Stanbury adds another factor to be considered (18). However, much remains to be discovered about the complicated mechanisms of calcium metabolism and its relationship to electrolyte depletion.

Asthenia and lassitude. Finally, asthenia and lassitude are the commonest symptoms in steatorrhea. Although non-specific they are both, nevertheless, symptoms of potassium depletion. Accordingly, it has become the practice of this clinic to give as routine therapy, potassium supplements, such as KCl 1-2 gm. t.i.d., whenever the patient is not well and to all patients with steatorrhea periodically.

SUMMARY

To conclude, there is evidence that patients with steatorrhea tend to get depleted of potassium. There is no evidence that the upsets in water excretion and electrolyte metabolism are other than secondary manifestations. However, in view of the widespread importance of potassium in a large variety of processes in the body, it would appear wise to maintain the potassium stores at normal levels.

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INTESTINAL UPTAKE OF VITAMIN B₁₂ IN THE MALABSORPTION SYNDROME

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It has been known for some time that liver extract and more recently vitamin B₁₂ are useful agents in the treatment of some patients with the malabsorption syndrome (1-4). Bioassay methods have revealed a low serum B₁₂ level in many of these patients (5). It has therefore been suggested that a defect in vitamin B₁₂ absorption is present in the malabsorption syndrome. In addition, actual malabsorption of vitamin B₁₂ has been demonstrated in patients with sprue (6-14).

VITAMIN B₁₂: CHEMISTRY AND QUANTITATIVE ANALYTICAL METHODS

In 1948 the crystallization of vitamin B₁₂ from liver was achieved (15). Biosynthesis was accomplished shortly thereafter utilizing the micro-organism *Streptomyces griseus* (16). This organism was employed in the production of radioactive vitamin B₁₂ by adding Co⁶⁰ to the culture medium (17).

Using x-ray crystallography techniques, Hodgkin (18, 19) has recently determined the complete structural formula of vitamin B₁₂ (Fig. 1). The empirical formula is C₆₃H₈₈O₁₄N₁₄PCo; the molecular weight is approximately 1350. The molecule resembles a porphyrin with a single central cobalt atom. Its shape is spherical with all of the chemically reactive groups located on the surface.

Among the available methods for measuring vitamin B₁₂ content are chemical techniques employing colorimetry, spectrophotometry or isotope dilution. Unfortunately, these methods fail to detect the low levels present in animal body fluids. They also fail to differentiate B₁₂-like substances from vitamin B₁₂. Bioassay techniques which measure the growth response of B₁₂-dependent bacteria or protozoa are far more sensitive although not entirely specific.

ABSORPTION, TRANSPORT AND STORAGE OF VITAMIN B₁₂

The main food source of vitamin B₁₂ is animal protein, particularly liver. It is present in certain forms of plant life as well. Smith believes that B₁₂ is derived from microbial synthesis in both of these sources (20).

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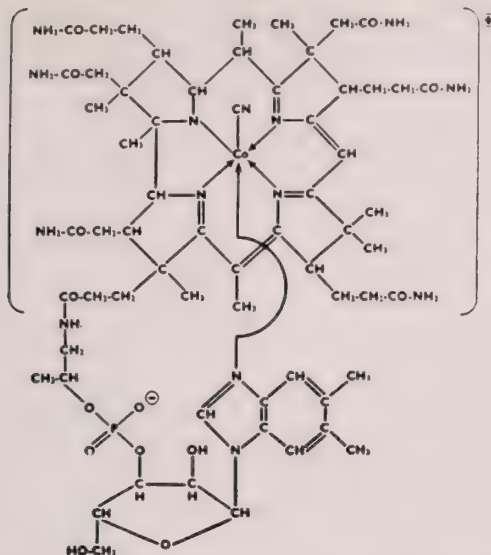


FIG. 1. Structural formula of vitamin B₁₂ as depicted by Hodgkin et al (18).

When food containing vitamin B₁₂ enters the stomach it encounters an as yet unidentified substance liberated by the fundic cells in the human being, termed by Castle intrinsic factor (IF). Although the specific mode of action of IF remains to be clarified, it is safe to assume that it is necessary for the absorption of dietary vitamin B₁₂. It is doubtful whether it plays a role in the absorption of the huge oral doses used in some studies (21, 22). By the use of tagged vitamin B₁₂ in patients with pernicious anemia, it has been shown that a stoichiometric relationship existed between the quantity of IF administered and the amount of B₁₂ absorbed in the dosage range of less than 1.0 μ g. of the vitamin (23). This phenomenon suggests a physico-chemical reaction. However, the rather limited ability of the small intestine to absorb vitamin B₁₂ beyond 1 μ g. amounts, regardless of the presence of abundant IF, has led Glass to postulate a "partial mucosal block" mechanism resembling the apoferritin system of iron absorption (24) (Fig. 2). In addition, there is a characteristic absorption delay after the ingestion of vitamin B₁₂ with peak plasma levels appearing 8 to 12 hours post-prandially (25) (Fig. 3).

Approximately 80 to 90 per cent of the circulating vitamin B₁₂ is bound to plasma protein. Studies employing both paper electrophoresis of serum and bioassay have located the bound B₁₂ with the alpha globulins (26). Intravenous injections of radio-active vitamin B₁₂ have demonstrated a rapid loss of isotope from the plasma with the accumulation of activity over the liver in 2 to 4 minutes (27). At the end of 6 to 10 days the major portion of absorbed vitamin B₁₂ is stored in the liver (28).

Only a small quantity of vitamin B₁₂ is eliminated into the urine. On the other hand, feces contain considerable amounts of B₁₂, derived both from the unabsorbed vitamin in food and from a portion synthesized by the bacterial flora of

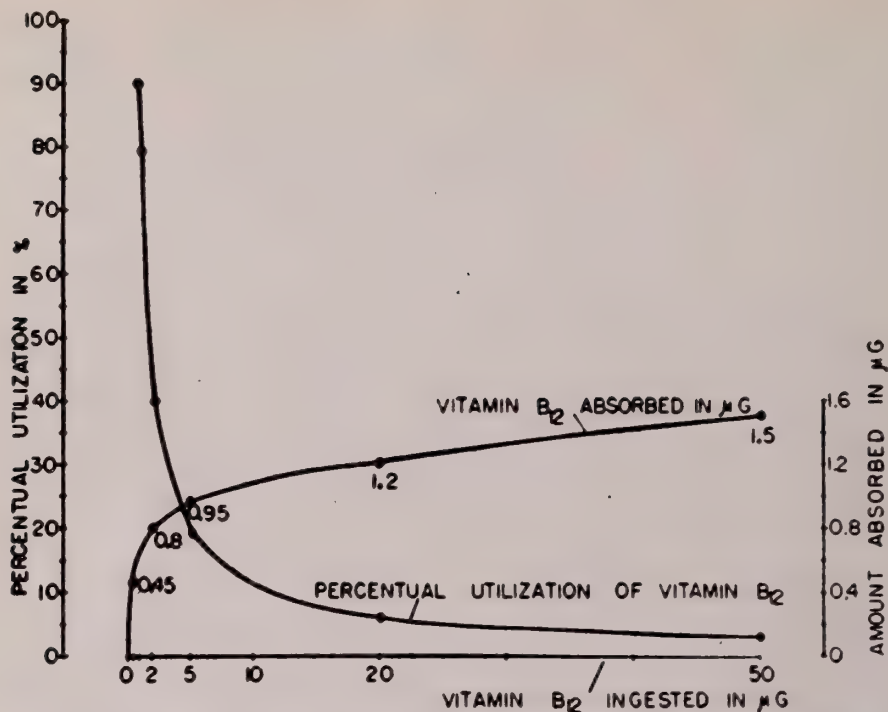


FIG. 2. The intestinal block to vitamin B₁₂ in normal humans as shown by the addition of increasing oral doses (0.5–50.0 μg.) of labeled vitamin B₁₂. Using the liver uptake method, Glass demonstrates the sharp fall in the percentage absorbed when more than 1.0 μg. B₁₂ is administered (36).

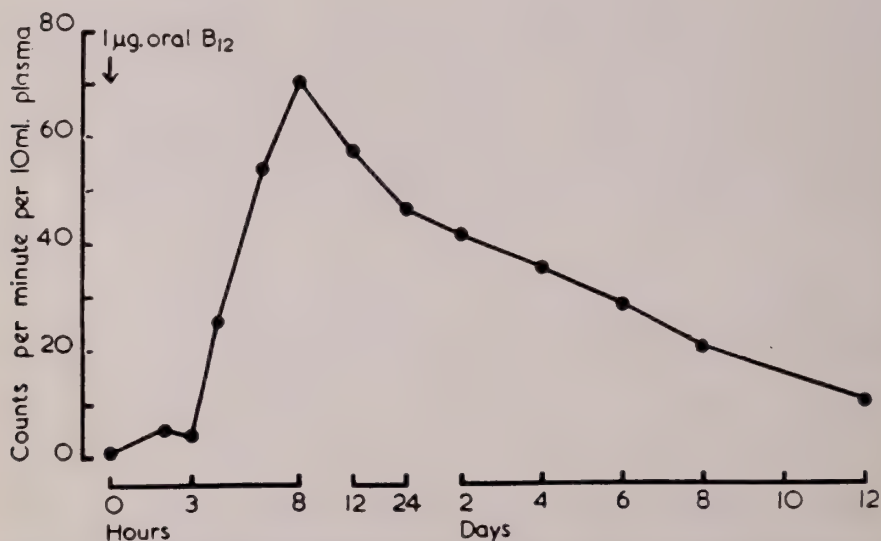


FIG. 3. Plasma radioactivity after an oral dose of 1.0 μg. of radioactive vitamin B₁₂ given to a control subject (25).

TABLE I
Vitamin B₁₂ Deficiency States in Relation to Site of Disturbance

Group	Site of Disturbance	Mechanism of Deficiency	Clinical State
A	Food	Deficient diet	Nutritional macrocytic anemia
B	Stomach	Deficient intrinsic factor	1. Pernicious anemia 2. Total gastrectomy 3. Gastric neoplastic infiltration
C	Small Intestine	Defective absorption	1. Idiopathic sprue 2. Sprue syndrome secondary to Whipple's disease, lymphoma, intestinal resection, strictures, diverticula or fistulae 3. Blind loop syndrome 4. <i>D. Latum</i> infestation
D	Miscellaneous	Metabolic defects	1. Liver disease? 2. Anti-vitamin?

the colon. This synthesized B₁₂ is probably unavailable to the host since B₁₂ absorption occurs almost exclusively in the small intestine. Table I shows the diseases of vitamin B₁₂ deficiency in relation to the supposed site of disturbance.

METHODS OF STUDYING THE INTESTINAL ABSORPTION OF VITAMIN B₁₂

1. *Hematologic response.* Castle's original method for the detection of the anti-pernicious anemia factor was based on the clinical and hematologic response of a patient with pernicious anemia in relapse following the oral administration of the test material. The same method may be applied to the absorption of vitamin B₁₂, but in addition to the difficulty in obtaining such patients, it has limited value as a quantitative technique. Further, the unpredictability of absorption in any given patient with pernicious anemia has recently been demonstrated by the observation that in certain patients in relapse as little as 5 µg. of vitamin B₁₂, administered orally without IF, resulted in a clinical and hematologic remission (29).

2. *Bioassay techniques.* Serum vitamin B₁₂ levels are abnormally low in the megaloblastic anemias (5). Attempts to devise a test of vitamin B₁₂ absorption based on serum bioassay methods have failed because when physiologic amounts of the vitamin are administered orally (1.0 µg. or less) no increase in serum vitamin B₁₂ content is demonstrable even in normal subjects. It is only when the oral dose of vitamin B₁₂ exceeds 500 µg. that the bioassay method reveals an increase in serum vitamin B₁₂ (21). Since patients with pernicious anemia absorb B₁₂ at these high dosage levels as well as control subjects, it would appear that under these circumstances absorption is independent of IF. Therefore, this method is useful in the detection of states of vitamin B₁₂ depletion, but not as an absorptive test.

TABLE II
Radioactive isotope methods to study intestinal absorption of B₁₂

Test Material or Site	Duration of Test	What Test Measures	Author of Test
Stool	7 days	Unabsorbed isotope	Heinle, Welch, et al., 1952 (30)
Urine	24 hours	Absorbed isotope "flushed" into urine	Schilling, 1953 (31)
Liver	6-10 days*	Absorbed isotope stored in liver	Glass et al., 1954 (32)
Plasma	8-12 hours	Absorbed isotope in plasma	Booth and Mollin, 1956 (25)

* Recently modified to a 48 hour test.

3. *Radio-active vitamin B₁₂*. Oral doses of B₁₂ labeled with Co⁶⁰, Co⁵⁸ or Co⁵⁶ have been the most useful tools for studying intestinal absorption (30-33, 25). The methods available at present are shown in Table II. The stool method is based on the assumption that whatever radio-activity has not appeared in the feces, during a standard collection period, has been absorbed. Although it is an indirect technique, it probably permits the most nearly quantitative estimation of vitamin B₁₂ absorption of any of the methods employed. The liver and plasma methods measure in a direct way a portion of the absorbed isotope. The former depends, among other factors, on the ability of the liver to store B₁₂. The urinary excretion method utilizes a 1000 µg. intramuscular "flushing dose" of non-radio-active B₁₂ to produce a diuresis of this vitamin. With the test performed in this manner, the 24 hour urine contains approximately one-third of the absorbed isotope-tagged B₁₂ (34).

METHODS AND MATERIALS

Clinical material. This report is based on a study of the following groups of persons:

Group 1. Control subjects: 12 females, 11 males, with no demonstrable disease of the gastrointestinal tract, hematopoietic system, liver or kidney.

Group 2. Pernicious anemia: 8 females, 7 males in whom the diagnosis was established on the basis of hematologic studies, gastric analysis and a typical response to vitamin B₁₂ therapy. There was no evidence of intestinal disease in this group.

Group 3. Idiopathic sprue: 16 females, 9 males, selected on the basis of a typical clinical picture with characteristic laboratory and roentgenologic findings of the malabsorption syndrome.

Group 4. Intestinal resections: 2 patients with a large portion of small intestine surgically removed in the treatment of jejuno-ileitis, and a third patient who had 90 per cent of the small bowel resected following occlusion of the superior mesenteric artery.

Laboratory methods. The following are the studies performed and the methods used:

1. Hematologic studies of bone marrow and peripheral blood.
2. Roentgen studies of the stomach, small intestine and colon.
3. Studies of intestinal absorption: oral glucose tolerance test; vitamin A tolerance test; serum carotene level; fecal fat partition; prothrombin time; serum Na, K, Cl, CO₂, Ca and P; serum iron; serum proteins and serum vitamin B₁₂ level.
4. Schilling test method, modified as follows:
 - a. All patients were studied in the early morning following a period of 12 to 16 hours of

TABLE III

Comparison of Schilling's original method and authors' modification of urinary excretion test

	Schilling's Method	Our Modification
Oral dose in $\mu\text{g.}$ of labelled B ₁₂	2.0	0.4-0.5
Interval between oral and "flushing" dose in hours.....	2	0
<i>Controls:</i>		
% of oral dose excreted in 24 hours	7-21	9-36
<i>Pernicious Anemia:</i>		
% of oral dose excreted in 24 hours	0-2.3	0-1.2
<i>Malabsorption Syndrome:</i>		
% of oral dose excreted in 24 hours		0-19.0

fasting. No vitamin preparations were permitted during the 48 hour period prior to and on the day of the test.

- b. 0.4 to 0.5 $\mu\text{g.}$ of radio-active vitamin B₁₂ tagged with Co⁵⁸ or Co⁶⁰ was administered orally in 75 to 100 ml. of water.
- c. 1000 $\mu\text{g.}$ of non radio active B₁₂ was injected intramuscularly immediately thereafter.
- d. In most of the persons under study, the test was repeated after one week or more, adding a 30 mg. dose of intrinsic factor concentrate along with the oral vitamin B₁₂. This IF material was of proved potency from a single batch of material* employed in each case.
- e. Patient was allowed only coffee and toast one hour after the test dose and a regular diet three hours after test dose and for the remainder of the day.
- f. A 24 hour urine collection was obtained.
- g. A 500 ml. aliquot was then added to a bottle of fixed dimensions and placed over a thallium activated NaI crystal scintillation counter. Then 25,600 counts were obtained of the unknown urine sample and compared with a water blank as well as with a radio-active standard solution obtained from the same isotope lot. When previous isotope administration had occurred, a urine blank was used. Results were expressed in percentage of administered dose excreted in the 24 hour urine.

It is evident that Schilling's original technique was modified in respect to the isotope dose and time interval between that dose and the administration of the non-radio-active vitamin B₁₂. The details of this modification and comparative results with Schilling's method are shown in Table III.

The use of a smaller oral dose (0.4 to 0.5 $\mu\text{g.}$) of B₁₂, with which dose the percentage absorption is greater than with the 2.0 $\mu\text{g.}$ dose, was made possible by the recent availability of radio-cobalt vitamin B₁₂ of high specific activity.

RESULTS

The urinary excretion of labeled B₁₂ is shown for all four patient groups in Figure 4. The 20 control subjects had an average of 17.9 per cent of the oral dose in their 24 hour urine with a range of 9.0 to 35.8 per cent. All 14 patients with pernicious anemia had excretions below 1.2 per cent. However, upon the addition of intrinsic factor, 13 excreted in the normal range with only one patient slightly below this range (6.3 per cent). In the group with idiopathic sprue, the average excretion was 3.6 per cent. Of these, 20 patients had marked impairment of B₁₂ urinary excretion, four had low normal results and the excretion of one

* Generously supplied by Abbott Co. Lot E-5872.

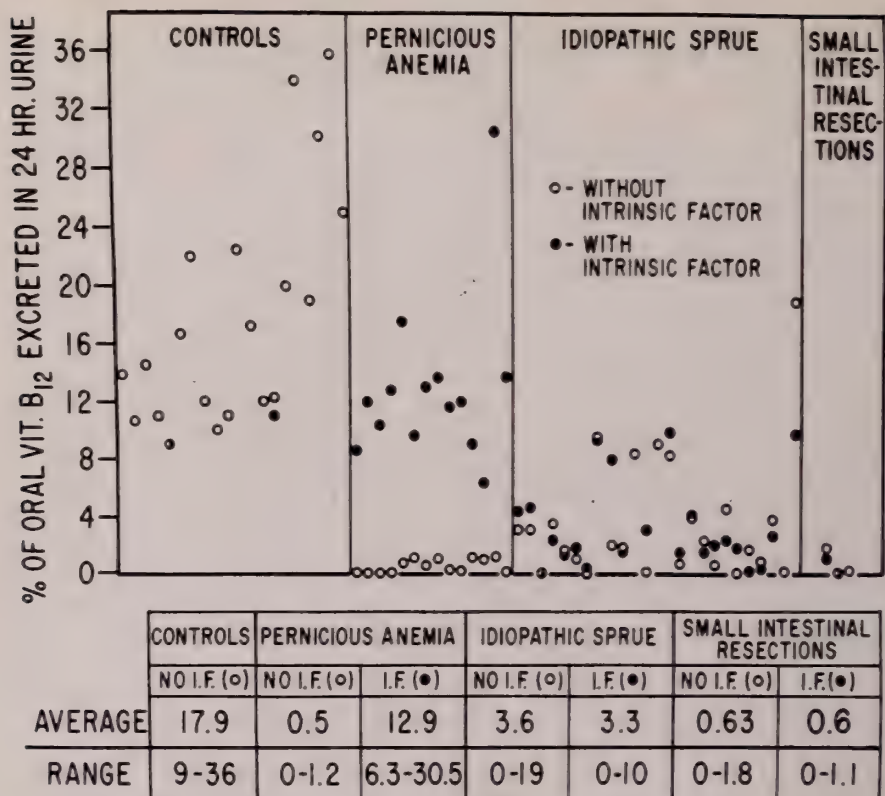


FIG. 4. Scattergraph of urinary excretion tests in control subjects as well as in patients with pernicious anemia, idiopathic sprue and extensive intestinal resections. The open circles represent the excretion of labelled vitamin B_{12} given orally. The closed circles represent the excretion of labelled vitamin B_{12} given orally *with* intrinsic factor. Each test on the same patient is placed in vertical alignment.

was in the normal range. The three patients with massive resections of the small intestine had virtually no detectable isotope in their urine. It is clear (Fig. 4) that intrinsic factor fails to improve the defective radio- B_{12} excretion in either idiopathic or secondary sprue.

Figure 4, therefore, demonstrates that the impairment in B_{12} absorption, as measured by the urinary excretion test, is less marked in most of the patients with the malabsorption syndrome than in the pernicious anemia group. Further, the characteristic improvement in vitamin B_{12} absorption achieved when a source of intrinsic factor is added to the latter group is lacking in the sprue patients studied.

DISCUSSION

In order to compare the results of this communication with those of previous reports it is necessary to contrast both the urinary excretion test method and the selection of patients for each clinical group. The use of a 0.4 to 0.5 μg . oral

dose of radio-cobalt vitamin B₁₂ has served to increase the average 24 hour isotope excretion of normal subjects (expressed as per cent) as compared with the 2.0 μ g. dose. Therefore, the smaller dose has widened the gap between the malabsorber and the normal-absorber. As stated above, Callendar and Evans (34) have shown that approximately one-third of the vitamin B₁₂ absorbed appears in the urine following a "flushing" dose. Therefore, the Schilling test may be used as a semi-quantitative index of vitamin B₁₂ absorption.

Regarding patient selection, there can be little disagreement concerning a precise diagnosis of pernicious anemia when all clinical and laboratory criteria are properly employed. On the other hand, the term "malabsorption syndrome" is applied to a variety of disease states. In this report we have included only a single type of secondary sprue, namely, that resulting from the surgical removal of large portions of the small intestine. All of the remaining patients fell into the category of idiopathic sprue; i.e., they presented at some time in their course with weight loss, diarrhea and steatorrhea—without evidence of a gross anatomic lesion in their small intestine. The symptomatology of these patients is discussed in more detail elsewhere in this symposium. In each patient there was laboratory evidence of an absorption defect for one or more nutrients besides vitamin B₁₂. Most of this group had the roentgenologic changes of the small intestine of the type seen in idiopathic sprue (35).

There is agreement among most authors that vitamin B₁₂ absorption is deficient in some patients with the sprue syndrome. However, since patients with different types of steatorrhea are included in the same statistical group by certain authors, the incidence of B₁₂ malabsorption varies among these reports. Thus in one group of 13 patients with steatorrhea, seven were found to have defective B₁₂ absorption, but among the malabsorbers there were two patients with diffuse diverticulosis (13). In another study of seven patients with sprue, four showed low levels of B₁₂ excretion without IF administration (9). Other smaller groups of patients have been reported which showed this defect in B₁₂ absorption as measured by the stool, urine or liver methods (7, 10, 11).

While most authors report no improvement in the vitamin B₁₂ absorption following the addition of IF in patients with sprue, it should be mentioned that Callender and Evans demonstrated an apparent enhancement of absorption by adding very large doses of IF (up to 2000 mg.) (13). However, in the same patients ordinary doses of IF (25 to 50 mg.), which were sufficient to correct the defective absorption of B₁₂ in pernicious anemia, failed to exert this effect.

The detection of a defect in vitamin B₁₂ absorption in a given case reduces the diagnostic possibilities to a limited group of gastrointestinal disorders. The disturbances related to stomach malfunction (Group B of Table I: pernicious anemia, gastric carcinoma and gastrectomy) are all corrected by the addition of IF, whereas the intestinal disturbances (Group C) are not improved by IF. The so-called "intestinal stasis" disorders (diverticulosis, strictures, blind loop syndrome) may show a return to normal B₁₂ absorption following antibiotic therapy, (14) thus adding another tool in the differentiation of vitamin B₁₂ malabsorption syndromes (Table IV).

TABLE IV
Differentiation of B₁₂ malabsorption states

	B ₁₂ alone	B ₁₂ + IF	B ₁₂ + antibiotics
Pernicious anemia . . .	poor absorption	improved	poor absorption
Sprue	poor absorption	poor absorption	poor absorption
"Intestinal stasis" syndrome	poor absorption	poor absorption	improved

SUMMARY

1. Recent advances in the chemistry and physiology of vitamin B₁₂ have been briefly reviewed.

2. A modification of Schilling's urinary excretion test was employed in the study of vitamin B₁₂ absorption in pernicious anemia and the malabsorption syndrome.

3. A severe defect in vitamin B₁₂ absorption was noted in all patients with pernicious anemia which was fully corrected by the addition of intrinsic factor.

4. Deficient vitamin B₁₂ absorption was noted in 20 of 25 patients with idiopathic sprue. In addition, 3 patients with a sprue syndrome secondary to the surgical removal of most of the small intestine similarly had defective absorption. Intrinsic factor failed to improve vitamin B₁₂ absorption in either group of patients with the malabsorption syndrome.

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THE PANCREATIC SECRETION IN THE MALABSORPTION SYNDROME AND RELATED MALNUTRITION STATES

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Despite great strides made by the application of esoteric biochemical methods, the physiology of the digestion and absorption of foodstuffs is not completely understood. Defective absorption of aliments in the small intestines may be due to a number of factors: 1. ingested agents antagonistic to the absorption of specific nutriments; 2. deficiency of enzymes necessary to degrade the food to the state in which it can be absorbed, e.g. pancreatic enzyme deficiency; 3. deficiency of adjuvant digestive juices whose absence interferes with the completeness of enzymatic digestion and emulsification, e.g. deficiency of bile or hydrochloric acid; 4. inadequacy of digestion time as seen in patients with rapid intestinal transit; 5. inadequacy of intestinal absorption surface as occurs in patients with massive small intestinal resection or bypass; 6. disruption of the processes whereby the foodstuffs actually pass from the intestinal lumen into the blood stream and lymphatics due, for example, to gross pathology of the small intestines as in widespread inflammatory disease, neoplastic infiltration (lymphosarcoma) and lymphatic blockade (Whipple's disease) or to undiscernible pathologic changes in the small intestines. This latter type of idiopathic malabsorption must be presumed to be caused by various vitamin, protein, or other deficiency states. The various pathogenetic factors are by no means independent. Indeed, the malabsorption state is usually of complex etiology, the extent of its complexity being realized only when the patient is subjected to the most careful physiologic studies.

This report is an analysis of the external pancreatic secretory function in the malabsorption syndrome (idiopathic sprue) and in other states characterized by malnutrition and malabsorption. The material is taken from a series of over 1500 patients studied with the secretin test technique (1). The grouping of cases is in accordance with the diagnosis upon discharge from the hospital.

METHOD

The secretin test is performed upon patients after a 12 hour fast. Under fluoroscopic control, a double-lumened gastroduodenal tube is placed with its tip at the ligament of Treitz. In this position, it is possible with continuous gentle suction to obtain quantitative, uncontaminated duodenal drainage. After an initial control collection period of 20 minutes, 1.0 clinical units of secretin per kilogram body weight is injected intravenously. Thereafter, the duodenal drainage is collected in divided 20 minute specimens for 80 minutes, the interval during which the submaximal stimulation of the pancreas is completely dissipated. The volume, the maximum bicarbonate concentration and the total amylase secretion are obtained in each test. These three factors characterize the pancreatic response to secretin. The diagnostic critical values for volume, bicarbonate and amylase have been

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The secretin used in this study was furnished by the Eli Lilly Company.

obtained from a statistical study of normal subjects (2). They are: 1. volume, 2.0 ml./kg. or more for 80 minutes—average 3.2 ml./kg.; 2. maximum bicarbonate concentration, 90 mEq./L. or more—average 108 mEq./L.; 3. total amylase secretion, 6.0 units/kg. or more for 80 minutes—average 14.2 units/kg.

RESULTS

Two types of pancreatic secretory defect have been described from the secretin responses of patients with pancreatic disease: 1. a quantitative deficiency in which there tends to be a reduction in volume flow with a maintenance of bicarbonate and enzyme secretion—a response characteristic of pancreatic duct obstruction as seen in neoplastic disease (3), and 2. a qualitative deficiency in which the volume secretion is sustained but the bicarbonate response and, to a lesser extent, the enzyme secretion is diminished—a response indicative of chronic inflammatory disease of the pancreas (2).

The results of the study have been summarized in Table I which presents the pancreatic secretion data of patients in whom malnutrition and/or malabsorption has been a clinical problem.

I. Non-Fatty Diarrheas of Various Origins. Patients with persistent, severe, non-fatty, non-bloody diarrheas may be suspected of having pancreatic disease. Sixty-six subjects with such diarrhea were studied. These heterogeneous diarrheas were associated with diabetic neuropathy, mucous colitis, biliary tract pathology, amebiasis, neurosis, or appeared as an isolated symptom. Of the 66 patients with non-fatty diarrheas, 52 had normal pancreatic secretion. Two patients, Cases 1 and 2, disclosed deficient secretion indicative of chronic pancreatic inflammatory disease, i.e. low bicarbonate response (2). Both patients lacked episodes of abdominal pain as well as a definite preceding history of acute pancreatitis. These are examples of the so-called silent or surprise pancreatitis recently stressed by Bartholomew and Comfort (4). There were 12 patients whose secretin test findings, i.e. low volume response, indicated pancreatic neoplasm (3), a diagnosis which in each instance was substantiated at operation. The combination of non-fatty diarrhea, mid-back pain, mild diabetes and weight loss forms a symptom complex most suggestive of carcinoma of the body of the pancreas, the confirmation of which diagnosis is hardly possible in the early stages without secretin test studies.

II. Sprue and Other Forms of Steatorrhea. Ninety patients with steatorrhea were studied. Of these there were 36 patients with the sprue syndrome. Thirty-three patients with sprue had normal pancreatic secretion; three subjects, Cases 3, 4 and 5, had abnormal responses to secretin. There was nothing in the clinical history of these three patients, e.g. duration, severity, or specific symptomatology, which distinguished them from the patients with normal pancreatic secretion. In Case 3 the defect in secretion was extensive, involving marked decreases in volume, bicarbonate and amylase secretion. This patient had a history of celiac syndrome in childhood, indicating the possibility of the malabsorption syndrome in childhood. On the other hand, the marked diminution of volume

TABLE 1

Secretin response data of patients with malabsorption syndromes and malnutrition states.
Abnormal values appear in italics.

Diagnosis	Total No. Cases	No. Cases Normal Panc. Secretion	No. Cases Abnormal Panc. Secretion	Secretin Response Data			
				Total volume secretion ml./kg.	Max. HCO ₃ secretion mEq. L.	Total amylase secretion u./kg.	Case no.
I. Non-fatty diarrheas	66	52	14				
A. Chronic pancreatitis			2	3.6 2.3	64 78	16.6 8.8	(1) (2)
B. Pancreatic cancer			12				
II. Steatorrheas							
A. Sprue syndrome	36	33	3	0.5 3.6 2.8	23 137 52	0.1 1.8 2.2	(3) (4) (5)
B. Chronic pancreatitis	9		9				
C. Cystic fibrosis pancreas	3		3				
D. Pancreatic carcinoma	8		8				
E. Diffuse jejuno-ileitis	4	2	2				
F. Organic malabsorption							
1. Massive S.I. resection	3	2	1	2.5	61	4.3	(6)
2. S.I. lymphosarcoma	4	4					
3. Gastro-ileostomy	2	2					
4. Jejunocolostomy	4	4					
5. Whipple's disease	1	1					
G. Idiopathic-etiology unknown	14	13	1	2.2	114	1.8	(7)
III. Jejuno-ileitis	26	18	8	3.6 4.2 5.6 1.2 3.2 2.9 3.8 2.5	96 42 95 86 101 60 104 61	2.8 1.9 2.0 9.2 3.8 4.9 3.0 4.3	(8) (9) (10) (11) (12) (13) (14) (15)
IV. Ulcerative colitis	39	35	4	2.1 1.5 1.6 0.6	50 67 71 74	10.8 0.7 7.5 6.5	(16) (17) (18) (19)
V. Peptic ulcer disease							
A. Gastric ulcer	26	24	2	2.0 3.2	54 42	8.9 0.7	(20) (21)
B. Duodenal ulcer	59	54	5	2.5 2.1 3.3 1.3 2.9	48 23 73 25 28	11.5 0.4 18.0 0.8 6.4	(22) (23) (24) (25) (26)
C. Post-gastrectomy disorders	21	14	7				
1. Dumping syndrome	5	4	1	3.2	60	17.9	(27)
2. Pain-diarrhea syndrome	4	2	2	4.1 2.8	59 45	1.2 16.2	(28) (29)
3. Steatorrhea syndrome	12	8	4	2.3 3.2 3.3 3.8	79 41 64 79	6.3 9.0 9.0 9.5	(30) (31) (32) (33)
D. Post-vagisection	16	16					
NORMAL SERIES.....	123						
Average.....				3.2	108	14.2	
Lower Limit Normal.....				2.0	90	6.0	

secretion suggests the alternate possibility of a mild cystic fibrosis of the pancreas surviving to adolescence.

Fourteen patients with malabsorption syndromes occurring in conjunction with recognizable disease of the small intestines were studied. Three of these were subjects with massive resection of the small intestines. In the two with mesenteric thrombosis and diffuse jejuno-ileitis, the pancreatic secretion was normal. One patient, Case 6, who had had a massive resection for diffuse jejuno-ileitis, displayed marked deficiency in bicarbonate and enzyme secretion as seen in pancreatic fibrosis. There were four patients with malabsorption syndromes due to lymphosarcoma of the small intestines; their pancreatic secretion was normal. In six patients, malabsorption was due to gastro-ileostomy or to jejuno-transverse colostomy. The pancreatic secretion was normal in all six cases. In the patient with Whipple's disease, the pancreatic response to secretin was normal.

The remaining 38 patients with steatorrhea displayed no evidence of absorption defect. There were nine patients with chronic pancreatitis, three with juvenile fibrocystic disease and eight patients with pancreatic cancer. In all these patients, abnormal pancreatic secretion was encountered, the defect varying with the type of pathology present. Six patients with steatorrhea had diffuse jejuno-ileitis; two of these, Cases 9 and 12, disclosed abnormal secretin tests. They are listed with the ileitis patients. There were 14 subjects with steatorrhea in whom no definitive diagnosis was made. Thirteen of these patients had normal secretin tests; one patient, Case 7, showed repeated evidence of an isolated enzyme defect. Isolated enzyme deficiency, i.e. lipase, has been previously reported by Diamond et al. in six of ten patients with idiopathic steatorrhea (5).

Steatorrhea is much more suggestive of pancreatic disease than non-fatty diarrhea. The steatorrhea is the result of a primary pancreatic enzyme deficiency in patients with chronic pancreatitis, fibrocystic disease and pancreatic cancer. In typical sprue and other malabsorption syndromes, the pancreatic secretion ought to be normal (2). Comfort et al. reported 13 patients with the sprue syndrome, in all of whom the secretin test was normal (6). Newsome, however, found two patients with abnormal pancreatic secretion in a series of seven patients with sprue (7). In the present series, three out of 36 patients with sprue had abnormal pancreatic secretion. The changes in secretion noted in these patients are diagnostic of a pancreatic fibrosis, the presence of which in sprue has been indicated by pancreatic pathology observed in post-mortem cases by Adlersberg and Schein (8).

III. and IV. Jejuno-Ileitis and Ulcerative Colitis. The secretin test was done in 26 patients with non-specific inflammatory disease of the small intestines, i.e. regional ileitis or diffuse jejuno-ileitis, and in 39 patients with non-specific inflammatory disease of the colon, i.e. ulcerative colitis. In the patients with ileitis, abnormal pancreatic secretion was encountered in eight subjects, Cases 8 to 15. It is to be noted that the deficiency is almost invariably in the enzyme secretion; three patients, Cases 9, 13 and 15, displayed low bicarbonate values; only one patient, Case 11, had a volume secretory defect. In the 39 patients with

ulcerative colitis, abnormal pancreatic secretion was seen in only four, Cases 16 to 19. The deficiency, unlike that in jejuno-ileitis, was not primarily in enzyme secretion.

V. Peptic Ulcer Disease and Post-Gastrectomy Syndrome. Data on 85 patients with peptic ulcer disease are presented as a basis for interpretation of the results obtained in the study of 21 patients with post-gastrectomy digestive complaints. Among the 26 patients with gastric ulcer, the pancreatic secretion was normal in 24. Two patients had abnormal secretion suggestive of pancreatic inflammatory disease. In these patients, Cases 20 and 21, chronic pancreatitis and pancreatic calcinosis were found at laparotomy. Of the 59 patients with duodenal ulcer, the secretin test findings were normal in 54. Five patients, Cases 22 to 26, showed the abnormal pancreatic secretion seen in chronic pancreatic inflammation.

Of the patients with post-gastrectomy digestive disturbances, intubation of the proximal duodenal loop through the gastroenterostomy was successful in 21 of the 30 patients in whom the secretin test was attempted. The successful intubations included five patients with dumping syndromes, four patients with abdominal pain and diarrhea, and 12 patients with steatorrhea. Evidence of pancreatic deficiency was found in all three groups. One of the five patients with dumping syndrome, Case 27, had test findings indicative of chronic pancreatitis. Two of the patients with pain and diarrhea, Cases 28 and 29, had similar abnormalities. Of the 12 patients with steatorrhea, eight had normal pancreatic secretion; four patients, Cases 30 to 33, had normal enzyme but low bicarbonate responses, an alteration of secretion indicative of pancreatic fibrosis. Sixteen patients with complete vagisection were studied with secretin. The pancreatic response was normal in all cases.

COMMENT

Precise diagnosis of digestive deficiencies requires procedures which evaluate three important variables: 1. the capacity for the production of digestive enzymes, 2. the duration of digestive activity—the intestinal transit time and 3. the capacity for the absorption of foodstuffs. Analysis of stool composition, though of some assistance in the differentiation of enzyme deficiency from absorption defect, is so sensitive to prolongation of transit time that many have raised doubts as to its preciseness as a diagnostic test (9). More reliable procedures include the various digestive tolerance studies. In these, serial determinations in the blood are done after the ingestion of a specific foodstuff and the results are compared with similar determinations made after the oral administration of a split product of that foodstuff. Thus, in the starch tolerance test (10), starch and glucose are given; in a protein tolerance test (11), gelatin and aminoacetic acid are employed; and in the fat tolerance studies (12), butter fat and vitamin A are given.

In the digestive tolerance tests, the absence of a blood response to the foodstuff, e.g. fat, in conjunction with an adequate elevation in the blood following oral administration of the basic substrate, e.g. vitamin A, is indicative of digestive enzyme (pancreatic) deficiency. On the other hand, lack of response to both

signifies an absorption defect. Clinical experience has shown that the digestive tolerance tests are more accurate in disclosing defects in absorption than as tests of pancreatic secretory capacity, a conclusion which appears to be equally valid for the newer digestive tolerance studies based upon the detection of radioactive atoms, e.g. I^{131} , in the blood, urine, or stool following the ingestion of an artificially prepared tagged substrate (13, 14). For these reasons complete evaluation of the etiologic factors in the malabsorption syndromes requires study of the external pancreatic secretion with secretin (9).

The frequency of pancreatic secretory deficiencies in patients with non-specific inflammatory disease of the intestines is noteworthy. Among the 26 patients with ileitis, eight patients had abnormal pancreatic secretion. The most consistent defect observed is in the enzyme secretion. In fact, five of these eight patients had isolated enzyme defects. Among the 39 patients with ulcerative colitis, there were four with abnormal secretion. Here the defect was in volume and bicarbonate as well as in enzyme secretion. Ball and others have commented upon the postmortem demonstration of unsuspected pancreatic fibrosis in patients with ileitis and ulcerative colitis (15, 2, 16). In no other group of patients studied with the secretin test has isolated enzyme deficiency been encountered with such consistency as in the patients with ileitis and jejunitis. Although the series is small, it is of interest that the defects in pancreatic secretion noted in the patients with sprue syndrome are similar to those seen in the jejuno-ileitis group, both of which are quite distinct from the more advanced defects observed in those patients with ulcerative colitis who displayed deficient pancreatic secretion. The British have been intrigued by the possibility of an etiologic relationship between sprue and jejuno-ileitis. Brooke, Cooke and Avery-Jones have reported cases of coeliac disease, sprue and idiopathic steatorrhea which have progressed to non-specific inflammatory disease of the intestines (17, 18).

The secretin test results in the cases of ulcerative colitis are in agreement with those reported by Lake (16), but mitigate against the hypothesis advanced by Portis (19, 20), i.e. that the ulceration in ulcerative colitis is due to the excessive proteolytic action of pancreatic ferments on a colonic mucosa rendered sensitive by high lysozyme titre. In none of the patients studied was there any evidence of hypersecretion of pancreatic ferments.

The abnormal pancreatic secretion observed in sprue, ulcerative colitis and jejuno-ileitis, correlated with the post-mortem demonstration of pancreatic fibrosis in these disorders, suggests an underlying nutritional etiology, most likely a protein deficiency state, an etiology of pancreatic fibrosis which has already been reported for other protein deficiency states (21, 22) and in the experimental animal (23, 24).

The development of peptic ulcer in patients with chronic pancreatitis and, particularly, the occurrence of diarrhea, steatorrhea and the dumping syndrome in subjects treated with gastrectomy for ulcer disease has implied to some an etiologic relationship between pancreatic inflammatory disease and the ulcer diathesis. The physiologic basis for such a relationship is clear insofar as the development of ulcer in pancreatitis; for here the absence of the neutralizing

effect of the pancreatic juice must result in unopposed duodenal hyperchlorhydria. Such a mechanism may also serve to explain the occurrence of marginal ulcers in patients following a radical resection of the duodenum and pancreatic head. The present series disclosed seven patients with chronic pancreatitis who had duodenal or gastric ulcers. The inverse hypothesis enunciated by Poth (25), viz. that uncomplicated peptic ulceration results from an inadequacy of pancreatic secretion, is not supported by the results of this study in which 78 of 85 subjects with ulcer disease had normal pancreatic secretion.

The digestive disturbances following gastrectomy may, not uncommonly, be due to pancreatic disorders. Vagisectomy, *per se*, does not appear to alter the pancreatic response to secretin (26), but the possibility exists that shunting the food across the duodenum may invoke a lesser elaboration of secretin than the passage of foodstuffs through this channel. Only a comparative study of patients with Bilroth I and Bilroth II operations can resolve this question.

Of five patients with dumping syndrome, one patient displayed evidence of pancreatic fibrosis. Among the group with persistent pain and diarrhea, two out of four showed evidence of chronic pancreatitis. The post-gastrectomy steatorrheas, which appear to have the laboratory findings of a sprue syndrome but which are refractory to regimens of vitamin B₁₂, folic acid and adrenocortical hormone, may upon investigation disclose evidence of a coexisting pancreatic etiology. One-third of these patients showed a pancreatic secretory defect. Pancreatic involvement may account for the relative refractiveness of the post-gastrectomy steatorrheas to sprue therapies.

CONCLUSIONS

The secretin test is of great value in the study of patients with the malabsorption syndrome and with malnutrition states. It affords a means of differential diagnosis between digestive disorders due to pancreatic secretory deficiency and those due to defective absorption of foodstuffs. In many instances the secretin test findings have indicated that the digestive disturbance is complex, involving both abnormalities of absorption and of pancreatic secretion.

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PATHOLOGIC STUDIES IN IDIOPATHIC SPRUE

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According to most observers there are no characteristic gross pathologic changes in primary sprue, whereas organic disease (e.g. lymphosarcoma, amyloidosis, Whipple's disease, etc.) is responsible for the malabsorption syndrome found in secondary sprue.

In the broader concept of idiopathic sprue, the disorder is considered to be a genetically-transmitted metabolic error, the focal point of which is intestinal malabsorption. According to this concept celiac disease in children, tropical and non-tropical sprue (idiopathic steatorrhea) are thought to be clinical manifestations of the same metabolic disorder triggered by a number of environmental factors such as infection, malnutrition or stress of tropical climates (1). One of the early observers of the disease, Samuel Gee in 1888, stated that "naked eye examination of dead bodies throws no light on the nature of the celiac affection" (2). Thaysen (3) believed that certain changes seen at autopsy in sprue patients could be attributed to post-mortem alteration, since the intestinal mucosa of sprue patients appears to be unusually susceptible to autolytic change. Adlersberg and Schein (4) in their study of six autopsied cases of primary sprue observed that several anatomical findings, while not necessarily characteristic or pathogenetically significant, were encountered at autopsy in cases of sprue. Atrophy of the small intestinal mucosa and villous deformities consisting of flattening and blunting of the villi (clubbing) as well as increased cellularity of the lamina propria were noted. The deformities of the villi were in one instance associated with stromal hyaline band formation near the tips of the villi (Schein (5)). These authors further describe instances of hemofuscinosis of the muscularis of the gastrointestinal tract, chronic mesenteric lymphadenitis with replacement of lymphatic tissue by hyaline and fibrous bands, centrolobular fibrosis of the liver and various degrees of pancreatic fibrosis (in the absence of biliary disease). Although it was apparent that these changes in the bowel and mesenteric lymph nodes were such as to impair absorption, the more fundamental pathogenetic implications were not clear.

Oehler (6) described the clinical and anatomical findings in seven patients with sprue, of whom four were considered to have idiopathic sprue. In this latter group there were marked changes in the small bowel consisting of chronic inflammation, ulceration, and fibrosis of the submucosa. Similar but somewhat less intense changes were seen in the colon. Some of the cases showed "severe nephrosis". Unfortunately, these cases are not too well documented as sprue in that there were no quantitative fat analyses of the stool and no absorption

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studies reported. Similar small bowel changes have been previously described in patients with primary sprue (7, 8, 9).

The utilization of biopsy techniques in living patients has permitted more detailed histological observation of the small bowel since rapid post-mortem autolysis causes changes which defy interpretation. Milanese et al. obtained a surgical biopsy of the jejunum in a case of tropical sprue in relapse (10). These authors observed atrophy of the villi and glands, increased cellular infiltration of the lamina propria and thickening of Auerbach's plexus. Paulley, utilizing surgical biopsies of the jejunum and mesenteric lymph nodes in patients with idiopathic steatorrhea, observed somewhat similar deformities of the villi and cell infiltration of the lamina propria (11). Butterworth has obtained a number of surgical jejunal biopsies in patients with tropical sprue at the time of operation for other disease (12). Atrophy of mucosa, clubbing of villi and increase of round cells and eosinophils of the submucosa were found in greater or lesser degree in these patients. Shiner has modified the Wood technique for obtaining gastric biopsies for duodenal and jejunal biopsies (13). This procedure appears to be a safe and clinically approved method for obtaining biopsies of jejunal mucosa. Her studies in sprue patients will be discussed elsewhere in this symposium (14).

The material of the present study includes 11 autopsies of patients with idiopathic sprue whose diagnosis was established by clinical and laboratory criteria. Six of these cases have been included in a previous report (4). In addition, jejunal biopsy material obtained by Dr. Margot Shiner, utilizing her jejunal biopsy technique from living sprue patients, is compared with the autopsy material.

CASE REPORTS

Case 1

A 48 year old Puerto Rican female was hospitalized in April 1931 with a four month history of weight loss, vomiting, diarrhea and fever. Her temperature was 103°F. The mouth was sore and the tongue was ridged. There were hemorrhages in both fundi. The liver and spleen both were palpated four fingers below the costal margins. Hemoglobin was 25 per cent, RBC 1.2 million per cu. mm., WBC 2500 per cu. mm. There was erythroid hyperplasia of the bone marrow. Following a blood transfusion, the temperature fell and vomiting and diarrhea ceased. Blood Wassermann and Kahn tests were four plus. Dysentery and typhoid-paratyphoid agglutinations were negative. Stool culture revealed *B. coli* and enterococcus. There was 13.5 per cent fat in the stool (low fat diet). Blood calcium was 8.5 mg. per cent. Free acid was present in the gastric contents. Liver extract and antiluetic therapy were given. Reticulocytes rose from 2 to 21 per cent in two weeks. There was a gain of 15 pounds in body weight during hospitalization.

She was then well until 24 hours before her last admission in September 1933, when she developed generalized abdominal pains, nausea and vomiting. There was no diarrhea. The abdomen was rigid throughout. Tenderness was most pronounced in the right lower quadrant. Blood examination showed WBC 4,200 per cu. mm. with 43 per cent polymorphonuclear cells, hemoglobin 49 per cent, RBC 2.25 million per cu. mm. At operation an acute appendicitis was found. There was no evidence of peritonitis. Post-operatively, the patient developed fever and signs suggesting bronchopneumonia. Despite oxygen and digitalization, the patient became increasingly dyspneic and expired on the third post-operative day.

Post-mortem examination revealed moderate generalized abdominal distention. There

was a herniated segment of transverse colon immediately beneath the appendectomy wound. There was 1000 ml. of this dark amber fluid in the peritoneal cavity. The small intestine was collapsed. The cecum and part of the transverse colon were distended.

The heart weighed 300 gm. There were a few small areas of fatty changes as well as minimal perivascular fibrosis. The combined weight of the lungs was 640 gm. The bronchi and bronchioles were filled with a tenacious thick red mucous. The liver weighed 1920 gm and had a greasy feel. Microscopically, there was fatty vasculolization in the mid-periphery of many lobules. The spleen weighed 490 gm. The cut surface was reddish-grey, firm and dry with prominent white pulp and trabeculae. Microscopically, the follicles were numerous. The pulp was congested and there was an increase in the reticulum and connective tissue throughout. The pancreas was normal. The kidneys together weighed 380 gm. There was slight congestion of the vessels. There was central autolysis of the adrenals. There was mild congestion of the esophagus. The gastric mucosa was atrophic. Microscopically, there was autolysis and atrophy of the glands. There was some increase in the mononuclear and plasma cells of the lamina propria. No information on the remainder of the intestines is available (autolysis).

Cause of death. Acute appendicitis.

Case 2

A 41 year old white female was hospitalized in July 1935 because of weakness, dyspnea on exertion and ankle edema of 3 months' duration. She had a history of celiac disease in childhood with diarrhea (5 to 6 stools daily) continuing all of her life. Examination revealed a deformed rachitic dwarf weighing 54 pounds. There was hemorrhagic retinitis, pallor and petechiae of the skin, smooth tongue, hepatomegaly and tenderness of all bones. Hemoglobin was 14 per cent (Sahli), RBC 820,000 per cu. mm., WBC 1950 per cu. mm. Bone marrow showed erythroid hyperplasia. Total protein was 5.7 gm. per cent. Serum calcium was 7.6 mg. per cent. Glucose tolerance test (oral) revealed a flat curve. Stool fat was 12.5 per cent of the dry stool weight (low fat diet). Treatment with iron, liver extract and transfusions resulted in improvement of all symptoms including diarrhea. Her symptoms gradually recurred however, and she was readmitted to the hospital two months later. A gastro-intestinal x-ray series showed distention of the small bowel and no other changes. Hemoglobin was 42 per cent. Blood transfusions were given and again resulted in improvement. At the time of discharge the hemoglobin was 72 per cent.

She was rehospitalized two days after discharge because of onset of vomiting of bright red blood, epistaxis and bleeding gums. Examination revealed carpo-pedal spasm, positive Chvostek and Trousseau signs, a large hematoma of the left buttock and thigh, ecchymoses, petechiae and bleeding gums. Hemoglobin was 46 per cent, RBC' was 2,080,000 per cu. mm., bleeding time was 5½ minutes, clotting time was 29 minutes. The diffuse severe hemorrhages could not be controlled with transfusions and calcium gluconate. After 10 days her temperature suddenly rose to 105°C. and she expired.

Post-mortem examination revealed numerous ecchymoses of the skin and multiple hemorrhages into the pleura, peritoneum, mucous membranes, anterior mediastinum and renal pelvis. The heart weighed 165 gm. The liver weighed 1240 gm. and showed some fatty changes. The pancreas revealed a small amount of interlobular fibrosis. The spleen weighed 150 gm. There was active hyperemia and hyperplasia of the lining epithelium of the sinusoids. The adrenals were normal. The kidneys weighed 220 gm. together. There was a diffuse pyelonephritic scarring. The esophagus was normal. The mucosa of the stomach was grossly flat and pale. The small intestine showed frequent areas of congestion. The duodenal mucosa was normal. The smooth muscle fibers of the muscularis contained large numbers of coarse, yellow-brown pigment granules which were distributed throughout the sarcoplasms. They did not give a positive reaction for iron. A similar but less marked granularity was seen in the muscularis of the jejunum and ileum. The remainder of the alimentary tract was without significant alteration.

The bone marrow was grossly spongy and red. Microscopically, there was a decided erythroid hyperplasia. The parathyroid glands were normal. The skin revealed a brown-green pigment in the basal layers of the epidermis. This pigment gave a negative reaction for iron.

Cause of death. Multiple hemorrhages.

Case 3

A 16 year old white male was admitted 10/30/43 for the first time because of abdominal pain and diarrhea of 3 months' duration. Because of persistence of abdominal pain, an exploratory laparotomy was performed. Enlarged hyperplastic mesenteric lymph nodes were the only abnormal findings. Hypoproteinemia, flat glucose and vitamin A tolerance curves and lymphocytosis of 65 per cent were discovered. Small intestinal series revealed segmentation of barium. Therapy including 2 transfusions, liver extract and vitamins resulted in some improvement although diarrhea (1 to 2 times daily) persisted. Four months prior to his final admission (7/8/44), he again began to vomit. Vomitus became coffee-ground in character and he suddenly became delirious and comatose on the day of admission. Examination revealed positive Trousseau's sign and convulsive movements of the body. There was bleeding from the mouth and rectum. Calcium was 5.5 mg. per cent. Bleeding time was over 20 minutes and clotting time was 15 minutes. Prothrombin index was less than 3 per cent of normal. Cephalin flocculation test was four plus. There was slight scleral icterus. The stool was grossly bloody and contained moderate numbers of fatty acid crystals. Coma rapidly deepened and the patient expired on the second hospital day.

Post-mortem examination revealed the body to be poorly nourished. There were numerous ecchymoses. The panniculus was brownish-yellow and thin. The stomach was markedly dilated. The small intestine and transverse colon were dilated. The mesenteric lymph nodes are moderately enlarged and soft. The heart weighed 175 gm. and was somewhat flabby. The lungs weighed 560 gm. There was generalized hyperemia. The liver weighed 1100 gm. and was quite soft. Section revealed a pattern in which the yellow periportal areas formed a slightly elevated rim above the dark red intervening areas. The parenchyma was friable. Microscopically, there was an extensive and severe parenchymal degeneration in which the dissociation of liver cells was striking. The individual cells were generally small and spindle-shaped. Many fat droplets were present. Mitotic figures were frequent at the periphery of the lobule. There was a striking infiltration of small round cells in these areas. The pancreas was normal grossly. There was some acinar atrophy. The spleen weighed 210 gm. There was marked congestion. The adrenals were normal. The right kidney weighed 200 gm. and the left 160. They were somewhat pale in color. The entire gastrointestinal tract contained blood. The esophagus was normal. The mucosa of the stomach and small intestines was atrophic, smooth and tan-colored. Microscopic examination of the stomach revealed slight atrophy and a mild infiltration of round cells in the mucosa and submucosa. The small intestinal villi were broad and clubbed. There were band-like deposits of hyaline material at the villous tips just beneath the basement membrane. There was a moderate polymorphonuclear leucocyte and eosinophil infiltration in the submucosa. The large intestine was not abnormal. The mesenteric nodes were normal. The bone marrow was normal except for some increase in fat. The pituitary was normal. The parathyroids were congested and hemorrhagic. The skin revealed an increase in the melanin-bearing chromatophores in the basal layers.

Cause of death. Liver necrosis and multiple hemorrhages.

Case 4

A 32 year old white female was observed at The Mount Sinai Hospital for a period of 12 years prior to her death. Her original admission at the age of 20 was for edema, associated with hypoproteinemia and hypocalcemia. A gastrointestinal series was interpreted as negative. One year later she was readmitted because of severe diarrhea. Gastric achlorhydria, hypoproteinemia and a flat oral glucose tolerance curve were found. At the age of

30 she had an attack of jaundice and fever. At the age of 31, she was again hospitalized for extreme weight loss, diarrhea and tetany. Steatorrhea (21.4 per cent of dry stool weight), flat vitamin A tolerance tests and hypoproteinemia were found. She was hospitalized for the last time in July 1944 for diarrhea, tetany and weight loss. Blood pressure was 120/86. Chvostek's and Trousseau's signs were present. The patient was poorly nourished. Hemoglobin was 80 per cent. A small bowel roentgen study revealed marked dilatation, segmentation of barium and hypersecretion. ECG showed myocardial involvement. Extrasystoles developed after I.V. calcium therapy. The serum albumin was 2.5 gm. per cent; globulin, 1.5 gm. per cent; Ca, 8 mg. per cent; P, 4.0 mg. per cent; alkaline phosphatase, 31 K-A units. Treatment consisted of liver extract, vitamins, adrenal cortical extract, transfusions, pancreatin, dihydrotachysterol and calcium gluconate. One day prior to her death, she developed a sore throat. On the final day of her life, she became stuporous. The blood pressure was unobtainable. Tetanic contractions, foaming at the mouth and involuntary defecation preceded death.

Post-mortem examination revealed the body to be extremely emaciated. The heart weighed 180 gm. The myocardium was brown and flabby. The lungs weighed 360 gm. There was focal emphysema and atelectasis. The liver weighed 2080 gm. The organ was yellow in color and greasy. There was a large amount of brown pigment in the Kupfer cells. The spleen weighed 75 gm. There was some degree of fibrosis microscopically. The pancreas was somewhat enlarged. There was a fine fibrosis throughout. The adrenals were normal. The kidneys were normal and of equal size (210 gm.). The esophagus was narrow and the stomach contracted and small. The gastric mucosa was atrophic. There was a submucous infiltration of round cells in the distal esophagus. There was a small myoma in the stomach. The small intestine appeared normal in every respect. There were two subserosal chondromas in the jejunum. The colon was normal. The mesenteric nodes were normal. Examination of the parathyroids revealed a conspicuous amount of connective tissue invading the parenchyma. The bone marrow was somewhat fatty. Examination of the brain revealed thrombosis of the superior sagittal sinus and cerebral veins.

Cause of death. Marantic thrombosis of dural sinus and cerebral veins.

Case 5

A 53 year old male was hospitalized on 4/21/46 because of low abdominal pain of six hours duration. He had been hospitalized two years previously because of diarrhea of 14 years' duration, carpo-pedal spasms and weight loss. Hypoproteinemia, hypocalcemia, flat vitamin A tolerance curve and barium meal studies consistent with diagnosis of sprue were found at that time. Treatment consisted of liver extract, vitamins, calcium and low fat diet and resulted in improvement. For four months prior to his final admission, he had symptoms of subacute obstruction of the large bowel. For the six hours prior to admission, he had severe lower abdominal pain, nausea and vomiting. Examination revealed a severely emaciated man in acute distress. There was marked abdominal distention and absent bowel sounds. There was marked clubbing of fingers. The hemoglobin was 61 per cent with 2450 WBC per cu. mm. The specific gravity of the urine was 1.005 with 1+ albumin and 4+ sugar. X-rays revealed obstruction of the large bowel. One day after admission, an operation was performed. A sigmoid volvulus was discovered. Sigmoidectomy and cecostomy were performed. Twelve days post-operatively urinalysis revealed many red blood cells. Seventeen days post-operatively the patient was catheterized because of bladder distention and regular catheterization was required for the remainder of his hospitalization. Temperature varied between 98 and 103.2°F. His course was progressively downhill with abdominal distention, cachexia, mental dullness, apathy and hallucinations. Urine revealed 5 to 12 red and white blood cells, a few granular casts and a trace of albumin. Patient expired 25 days post-operatively.

Post-mortem examination revealed numerous adhesions between loops of small intestine and abdominal wall. The abdominal contents were matted together. There was no excess of peritoneal fluid. There was dilatation of the stomach and small intestine. The dilatation

was massive in the stomach and proximal jejunum but decreased distally. A cecostomy was found in the right lower quadrant. The sigmoid colon had been resected. The mesentery contained numerous, soft, pale brown lymph nodes, the largest of which was 2 cm. in diameter. The heart weighed 300 gm. There was some atrophy of the myocardial bundles and minimal myocardial fibrosis. The lungs together weighed 2075 gm. They were heavy and darkened throughout. There was a severe generalized hyperemia and intra-alveolar hemorrhage. There were focal areas of bronchopneumonia. The liver weighed 1875 gm. and showed central lobular congestion. There was a fine diffuse intralobular fibrosis of the pancreas. The spleen weighed 190 gm. There was marked congestion of the pulp and sinusoids. The adrenals were of average size and showed diffuse post-mortem autolysis. The surface of the kidneys was studded with small, soft, yellow elevations with thin hemorrhagic margins. There were many yellow streaks throughout the cortex and medulla and a number of small abscesses. Microscopically, there was acute pyelonephritis with abscess formation.

The wall of the esophagus was diffusely edematous. There was a severe acute ulcerative esophagitis. There was hemofuscin pigmentation of the smooth muscle. The gastric mucosa was grossly normal but revealed microscopic evidence of hyperemia and acute inflammation of the lamina propria and pigmentation of the muscularis. There was a distinct gross pigmentation of the small and large bowel directly beneath the serosa. This pigmentation was diffusely present but was not as intense in the ileum. The duodenum revealed microscopic evidence of acute inflammation of the submucosa. There was blunting of the villi of the jejunum and ileum. There was a diffuse hemofuscinosis of the muscularis mucosa in the entire small bowel and colon. There was an acute necrotizing proctitis. The bone marrow was hyperplastic. The skin revealed a diffuse grey-tan pigmentation. There were a moderate number of large cells containing much brown granular pigment. Some cells gave a positive staining reaction for iron and others for hemofuscin.

Cause of death. Volvulus of the sigmoid with resection; acute pyelonephritis with abscess formation.

Case 6

A 53 year old white female was admitted for the first time in 1937 because of severe anemia and diarrhea. The hemoglobin was 23 per cent with 1.7 million RBC per cu. mm. Splenomegaly, achlorhydria and koilonychia were found. Transfusions and iron and hydrochloric acid therapy restored the hemogram to normal. A diagnosis of achlorhydric hypochromic microcytic anemia was made. She was then well until six months prior to her second admission in 1943 when she developed diarrhea, weakness and weight loss. Hepatosplenomegaly and bleeding hemorrhoids were found. The hemoglobin was 59 per cent with 4.4 million RBC per cu. mm.; the glucose tolerance curve was flat. A diagnosis of non-tropical sprue and chronic blood loss from bleeding hemorrhoids was made. Hemorrhoidectomy was subsequently performed. She was admitted for the fourth time in 1945 because of recurrence of severe diarrhea (8 to 10 times daily). Stools were repeatedly positive for occult blood. The serum Ca was 7.4 mg. per cent; vitamin A and glucose tolerance curves were flat. The stool contained fat and undigested food particles. She responded to treatment consisting of pancreatic extract, blood transfusions and I.V. Amigen. Forty-eight hours before her final admission in November 1945 she developed a dry cough. The following day she noted fever and dyspnea. On the day of admission she became cyanotic, extremely dyspneic and stuporous with temperature of 104°F. There was a loud inspiratory stridor with inspiratory retraction of the supraclavicular regions. Bronchoscopy revealed laryngeal and tracheal edema. The patient improved markedly after this procedure only to have another attack of laryngeal edema and expire suddenly.

Post-mortem examination revealed extensive edema and congestion of the lungs with a small area of bronchopneumonia in the right upper lobe. The bronchial mucosa was reddened. There was marked laryngeal edema. The tracheal mucosa was deep red with greyish areas of surface necrosis. Microscopically throughout the lung there was a widespread

exudate of blood and large mononuclear elements. There was a perivascular and peribronchial cuffing of round cells and leucocytes. The bronchial epithelium was almost completely missing. The heart weighed 300 gm. Its muscle was brown and showed areas of fibrosis and lipomatosis. The liver weighed 1580 gm. and had a normal consistency. There were many leucocytes in the periportal spaces. The spleen weighed 300 gm. and was coarsely lobulated. The cut surface revealed a congested pulp with discernible landmarks. The pancreas showed scattered intralobular fibrosis. Examination of the adrenals revealed some central autolysis. The kidneys weighed 350 gm. There was sclerosis of the larger renal arteries. The bone marrow was normal.

The stomach and intestines were markedly dilated. The esophagus was normal. The stomach showed a mucosal polyp the size of a pea near the pylorus. The mucosa of the small and large bowel was normal in every respect grossly. The mucosa of the antrum and fundus was slightly lower than normal. There were many plasma cells and leucocytes in the lamina propria. In the small intestine, there was a slight increase of plasma cells and polymorphonuclears in the lamina propria. There were a number of enlarged lymph nodes in the mesentery. Microscopically there was a diffuse fibrosis of these nodes.

Cause of death. Acute necrotizing laryngotracheitis (influenza virus B).

Case 7

A 59 year old white female was hospitalized in July 1950 because of diarrhea, gaseous eructations and abdominal bloating. Five years previously she began to suffer from nausea and vomiting associated with a 50 pound weight loss. Cholecystectomy was performed in 1947. Following this procedure, she was somewhat improved but still had frequent eructations, bloating and bouts of vomiting. She had had chronic bronchitis with a cough productive of mucopurulent sputum for many years. Vomiting was usually preceded by coughing and gagging. Four months prior to admission her symptoms became somewhat more severe and were now associated with diarrhea (10 to 12 watery, light-yellow stools daily). The blood pressure was 115/75. Wheezes were heard throughout the chest with some prolongation of the expiratory phase. There was a grade III precordial murmur heard best at the apex. The liver was felt one finger's breadth below the right costal margin. There was clubbing of the digits. The hemoglobin was 11 gm. per cent; WBC 9,800 per cu. mm. Congo red test was negative. The total proteins were 4.8 gm. per cent with albumin 2.2 and globulin 2.6 gm. per cent. Stools contained 45 per cent fat, mainly fatty acids with some neutral fat. Prothrombin time was 23 seconds. The blood calcium was 6.4 mg. per cent. Pancreatic function studies were normal. Gastrointestinal x-ray series showed a normal stomach and duodenum. There was flocculation and segmentation of barium in the small bowel. Vitamin A tolerance tests done before and after the administration of cortisone and ACTH revealed a flat curve. An oral glucose tolerance test revealed a flat curve, whereas the intravenous glucose tolerance test was normal. Therapy, consisting of high caloric-low fat diet, vitamins, liver extract and cortisone (100 mg. daily for 15 days), did not alter the clinical course. ACTH, given intramuscularly for 15 days, likewise did not produce significant benefit. She developed abscesses of the buttocks at the sites of ACTH injections. These were drained and the patient was discharged. Two weeks later she was admitted to another hospital because of marked exacerbation of diarrhea, vomiting and weight loss. She developed a lobular pneumonia while hospitalized. In spite of all therapy, the patient's course was progressively downhill and she expired on February 21, 1951.

Post-mortem examination revealed the body to be markedly emaciated. The panniculus was minimal in amount. There was a large area of consolidation in the left lower lobe and smaller areas in the right upper and lower lobes. There was calcification of the mitral ring and the aortic cusps with stenosis of the aortic valve. The liver was of average size and appeared grossly normal. The pancreas was small and somewhat fibrotic. The spleen, kidneys and adrenals were grossly normal. The stomach was markedly dilated with thin but intact mucosa. The duodenum was markedly dilated and had a pale greyish-white mammilated mucosa. There were many various sized irregular areas which were hemorrhagic

and possibly superficially ulcerated. The remainder of the small intestine was normal. The mesenteric lymph nodes were greatly enlarged, soft, pale yellowish-pink in color. The mucosa of the large intestine was intact and for the most part thin and atrophic. In the transverse colon, the mucosa was irregular in thickness and often granular in appearance.

Microscopic examination revealed confluent lobular pneumonia, fatty degeneration of the myocardium, fatty infiltration and cloudy swelling of the liver and acute splenitis. There was atrophy of the mucosa of the stomach. The duodenal mucosa revealed several areas of superficial necrosis affecting only part of the folds or glands in most places. In a few, however, the mucosa was destroyed for its entire thickness, the bare submucosa covered with fibrin enmeshing cellular debris. In none of these areas was any inflammatory reaction or cellular infiltration of the supporting stroma noted. The submucosa was rich in distended and congested blood vessels. There were several small areas of superficial necrosis in the ileum with evidence of cellular reaction. The mucosa was atrophic throughout both ileum and colon. The normal architecture of the mesenteric nodes was preserved. The sinusoids were dilated and filled with large and small lymphocytes and desquamated epithelial cells. The follicles were large and numerous with prominent germinal centers.

Cause of death. Confluent bronchopneumonia, emaciation.

Case 8

A 38 year old white female was hospitalized for the third time in January 1951, because of diarrhea of one month's duration. She was first hospitalized at the age of 28 in 1934 because of diarrhea, abdominal distention and weight loss. Findings at that time included a fecal fat of 48 per cent. There was generalized osteoporosis. Gastrointestinal x-ray study was interpreted as showing a masked diffuse inflammatory process in the lower jejunum and entire ileum. She developed a Brown-Sequard syndrome at D₁₀₋₁₁. The cause of this neurological complication, which cleared spontaneously, was not ascertained. Treatment resulted in some improvement in the sprue syndrome. She was again hospitalized in 1943 because of exacerbation of symptoms. Treatment with a high calorie-low fat diet, vitamins and liver extract resulted in a marked improvement. One month prior to her final admission, symptoms again became severe. On examination, she was emaciated and chronically ill. The abdomen was distended and thin-walled with visible peristalsis. There was clubbing of the digits. An oral glucose tolerance test revealed a flat curve. A gastrointestinal x-ray series revealed dilated loops of small intestine with thickening of mucosal folds, segmentation and flocculation of barium and prolonged transit time. She was persistently nauseated with frequent vomiting and abdominal cramps. Tube feedings were carried out with some success. Vitamins, calcium and analgesics were given. On the seventeenth hospital day, the patient complained of increasingly severe abdominal pain and increased vomiting. On the eighteenth hospital day she went into shock and expired.

Post-mortem studies showed an emaciated body. The abdomen was markedly distended. There was 1000 ml. of clear sero-sanguinous fluid in the abdomen. There was a huge, dilated, dark-red, redundant loop of bowel which arose from the left lower quadrant and extended to the right upper quadrant. This loop represented a volvulus of the sigmoid. The small intestine was moderately dilated and pale. The stomach was not dilated. The heart weighed 190 gm. There was evidence of old healed mitral valvulitis. The lungs together weighed 650 gm. and were grossly normal. The liver weighed 1370 gm. It was very flabby with a smooth surface and rounded edge. The spleen weighed 45 gm. Grossly and microscopically, the organ was normal. The adrenals were normal grossly. The pancreas was normal. The kidneys revealed old pyelonephritic scarring. The esophagus was normal. The stomach was not dilated. The mucosa was thin and the rugae flattened. The jejunum and ileum were dilated and the mucosa was less velvety than usual. Microscopically, there was such autolysis that it was difficult to interpret the sections. However, the mucosa appeared atrophic and the villi broadened. In many of the muscle fibers of the muscularis layer of the small bowel there was a granular pigment which did not stain as iron. The colon to the area of volvulus

was moderately dilated. The lumen of the twisted sigmoid was filled with dark old blood and gas. The mesenteric lymph nodes showed fibrous cords in the sinusoids. The bone marrow appeared normal grossly.

Cause of death. Acute intestinal obstruction secondary to volvulus of sigmoid.

Case 9

A 51 year old white female was hospitalized in February 1951 because of weight loss and diarrhea. For the previous 11 years she had had recurring episodes of diarrhea consisting of 10 to 20 bulky, foul-smelling bowel movements daily. Treatment with vitamins and liver extract resulted in improvement. Three months before admission she began having frequent attacks of carpo-pedal spasms. Examination revealed a thin, chronically ill female. The abdomen was distended with visible peristalsis. Trousseau and Chvostek signs were positive. The hemoglobin was 9.5 gm. per cent with a hematocrit of 29 per cent and 2,186,000 RBC. The oral glucose tolerance test was flat. There were large quantities of neutral fat and fatty acids in the stool. X-ray examination of the gastrointestinal tract was not diagnostic. Serum calcium ranged from 5.1 to 7.2 mg. per cent. Bone marrow revealed a megaloblastic picture. Treatment, consisting of calcium, vitamin B₁₂ and folic acid, resulted in little or no improvement. She developed several severe crises of abdominal distention, the last one on the twenty-seventh hospital day, was refractory to any therapy. She went into shock and expired.

Post-mortem examination revealed an emaciated body. The abdomen was distended. There was a healed scar of a right radical mastectomy. The small and large bowel were markedly distended by gas and feces. The distention ceased abruptly at the splenic flexure but no obvious cause for this phenomenon was found. There were no adhesions and the serosa was smooth and shiny. There was no fluid in the peritoneal cavity. The heart weighed 175 gm. and was grossly normal. The lungs together weighed 680 gm. There was emphysema as well as focal atelectasis. The spleen weighed only 25 gm. The organs were otherwise normal grossly and microscopically. The liver weighed 1150 gm. and revealed on section the normal architecture and scattered yellowish foci .1 to .3 cm. diameter. There was moderate generalized congestion.

The pancreas was normal grossly. The adrenals likewise appeared normal. The kidneys together weighed 221 gm. There were no gross or microscopic abnormalities. The esophagus was normal. The stomach was moderately dilated by gas and undigested food. The mucosa was slightly flattened. The duodenum was moderately dilated and the mucosa reddened. The remainder of the small intestine was markedly dilated. The mucosa appeared normal grossly. There were scattered bullae of air beneath the mucosa in some areas. The large bowel showed similar features. The marked dilatation extended to the splenic flexure. Microscopically, the mucosa of the small and large intestine was without change. The villi were not clubbed or atrophic. There was no pigmentation of the musculature. The descending colon and rectum were normal. The mesenteric lymph nodes were slightly enlarged; microscopically, there was accentuation of the connective tissue septa. The vertebral bodies showed severe osteoporotic changes. The trabeculae were thinned. The bone marrow was grossly normal.

Cause of death. Acute dilatation of the intestine, volvulus?, angulation?.

Case 10

A 67 year old white male was first hospitalized in February 1955 because of diarrhea of eight years' duration. The stool was watery, brown and occasionally accompanied by abdominal cramping. He had lost 12 pounds in the previous year. On examination, he was emaciated and there was some abdominal distention. There was clubbing of the fingers and toes. Examination of the blood revealed: hemoglobin, 13.9 gm. per cent; total protein, 5.4 gm. per cent; albumin, 3.3, and globulin, 2.1 gm. per cent; fasting blood sugar, 75 mg. per cent; calcium, 8.5 mg. per cent; phosphorus, 2.2 mg. per cent; stool fat, 66.4 per cent of dry weight (40 per cent fatty acid and 26 per cent neutral fat). An oral glucose tolerance

test was flat. A gastrointestinal roentgen series was interpreted as showing changes most consistent with a granulomatous process involving the stomach, duodenum and jejunum. Gastroscopy was normal. Treatment, consisting of high protein diet and vitamins, resulted in some improvement and the patient was discharged. Diarrhea continued, averaging six movements daily. The patient again began to lose weight. He was readmitted in August 1955 in a state of extreme emaciation. Blood studies were as follows: hemoglobin, 11.8 gm. per cent; WBC, 10,000 per cu. mm.; Ca, 6.8 mg. per cent; P, 3 mg. per cent; K, 1.8 mEq./l.; Na, 148 mEq./l.; chloride, 115 mEq./l. Therapy, consisting of intravenous fluids, electrolytes, intravenous ACTH and albumin, were unavailing and the patient expired on the third hospital day.

Post-mortem examination revealed a badly emaciated body. There was clubbing of the fingers. The abdominal wall was very thin with no panniculus. There was a small amount of serous fluid in the abdominal cavity. The heart weighed 190 gm. The myocardium had a slightly brownish color. There was moderate atherosclerosis of the aorta. The lungs together weighed 1500 gm. On cut section, the lungs were reddened and much clear fluid was expressed. The trachea and bronchi contained frothy fluid. The liver weighed 800 gm. On cut section the lobular architecture was normal. The spleen weighed 82 gm. On cut section the usual architecture was apparent. The pancreas was grossly normal. The adrenals were grossly normal. The kidneys together weighed 222 gm. and were grossly and microscopically normal.

The esophagus was normal in caliber and had a smooth, intact mucosa. Microscopically, there was a mild round cell infiltration of the submucosa. The stomach was slightly dilated but its mucosa appeared normal. The duodenal mucosa was brownish-red in color with submucosal hemorrhages and congestion seen microscopically. The jejunal and ileal bowel wall was very thin and the mucosa was atrophic. Microscopically, there was absence of villi and glands with vacuolar degeneration of the musculature. The colon was normal in all respects. The mesenteric nodes were not enlarged. The bone marrow was scanty.

Cause of death. Cachexia.

Case 11

A Canadian-born, white, male, who was 38 years old at the time of his death in 1954, had been well until 1950 when he noted onset of frequent bulky stools, abdominal cramps and weight loss. Six months later, he was hospitalized because of the passage of large quantities of bright red blood by rectum. The cause of the bleeding was not ascertained. Because of the persistence of diarrhea and weight loss he was admitted to The Mount Sinai Hospital for the first time in February 1951. Total fecal fat was 33.5 to 46.1 per cent of dry stool weight. Glucose tolerance and vitamin A tolerance test curves were flat. Gastro-intestinal x-ray series revealed flocculation and segmentation of barium, thickening of mucosal folds and dilatation of many loops of small bowel. Pancreatic secretin studies were normal. A diagnosis of primary sprue was made and the patient was treated with a low-fat diet, parenteral and oral folic acid and vitamin B₁₂ with some improvement.

Two months later, he had an unexplained attack of abdominal pain and fever which subsided after a few days of conservative therapy. In June of 1951, because of exacerbation of his diarrhea and weight loss, corticotropin was started. Subsequently, cortisone was substituted for ACTH. He did well on this therapy until July 1953 when he again experienced an attack of abdominal pain thought to be consistent with an intestinal perforation but treated conservatively. In August 1953 he had another episode of intestinal bleeding. In March 1954 he experienced a third attack of severe abdominal pain and fever. With each attack of pain or bleeding, cortisone was temporarily withheld. In April 1954 he experienced another attack of massive gastro-intestinal bleeding for which a subtotal gastrectomy was performed. Cortisone was withheld but reinstituted because of recurrence of diarrhea. An attack of abdominal pain thought to be due to intestinal perforation occurred in July 1954. Two weeks later, bleeding recurred and a revision of the gastrectomy was performed. From this point until his death in September 1954 his course was one of progressive cachexia.

Steroid therapy caused some improvement from time to time but invariably was followed by bleeding or abdominal crises (? perforations).

Post-mortem examination revealed anasarca and emaciation. There was 500 ml. of clear amber fluid in each pleural cavity and 800 ml. of similar fluid in the abdominal cavity. There were numerous fibrinous peritoneal adhesions. A subtotal gastrectomy and gastroenterostomy had been performed. There was a perforation of the jejunum adjacent to a left sub-diaphragmatic abscess cavity. There was a 1 cm. embolus in the right pulmonary artery occluding the middle lobe branch. The middle lobe was infarcted. There was moderate edema throughout the remainder of the lungs. The heart weighed 340 gm. There was an excess of pericardial fluid. The left ventricular wall was slightly hypertrophied. There was a small amount of brown pigmentation scattered throughout the myocardium microscopically. The aorta showed minimal atherosclerotic changes. There were thromboses of both iliac veins. The spleen weighed 230 gm. Microscopically, there was congestion and an increase in plasma cells. The liver weighed 2400 gm., was extremely friable and had a greasy appearance. There was marked centrilobular congestion. There was a heavy cellular infiltrate consisting mainly of polymorphonuclear leucocytes in the periportal area. The pancreas weighed 80 gm. and was normal grossly and microscopically. The adrenal cortex was exceedingly thin and almost white in color. The layers of the cortex were not well defined microscopically. The zona fasciculata was particularly indistinct. There was moderate congestion. The esophagus was normal. The remaining gastric pouch had an extremely thin and friable wall. The mucosa was somewhat atrophic. There was marked post-mortem autolytic change in the stomach. The wall of the small intestine and proximal half of the colon was extremely thin and friable. Throughout the duodenum, jejunum and proximal ileum there were numerous shallow ulcerations in the mucosa measuring 0.5 to 3.0 cm. These ulcers were extremely ragged with many having a necrotic zone and raised edges.

The majority of the lesions, however, were simply irregular defects in the mucosa without secondary defects in the mucosa and without secondary inflammatory change. One of the jejunal ulcerations had perforated at the site of the abscess cavity. There were several areas throughout the jejunum where the bowel wall was thick and reddened for distances up to 15 cm. The gross appearance of these areas suggested jejunitis. The mucosa of the colon showed no evidence of ulceration or erosion. The mesenteric lymph nodes measured 0.3 to 1.5 cm. and were moderately firm and dark brown. The mesentery was slightly thickened and revealed many yellow streaks running from the bowel toward the root. Microscopically, the small bowel revealed flattening of the mucosa and extensive autolytic change. In some areas, there was an increase in the cellular composition of the sub-mucosa. The ulcer beds contained a moderate number of polymorphonuclear leucocytes. In some areas, there was an eosinophilic smudging of the arterial walls. In the thickened areas of jejunum, there was thickening, fragmentation and fibrinoid change of the musculature. There was a moderate diffuse cellular reaction consisting of macrophages, lymphocytes and a few segmented lymphocytes. Autolytic change in the colon was extensive. Many of the mesenteric vessels and lymphatic capillaries were surrounded by small collection of round cells. There was a small amount of fibrinoid material surrounding many of the lymphatic vessels. The mesenteric lymph nodes were almost completely replaced by a large amount of fibrinoid and fibrous material. A few small follicles remained. Examination of the urinary tract revealed a mild focal pyelonephritis. The pituitary was normal.

Cause of death. Cachexia, gastrointestinal bleeding, pulmonary infarction.

POST-MORTEM FINDINGS IN IDIOPATHIC SPRUE

In the eleven cases presented above, the cause of death was directly or indirectly related to the sprue syndrome. All but three of the patients died during a period of relapse. Of those in remission at the time of death, one died following appendectomy for acute appendicitis (Case 1), another of acute yellow atrophy (Case 3) and a third of necrotizing tracheo-bronchitis (Case 6). Of the eight pa-

TABLE I
Summary of findings at autopsy

Case	Stomach	Small Intestine	Large Intestine	Mesenteric Lymph Nodes	Pancreas	Liver	Spleen	Bone Marrow	Adrenals	Parathyroid	Skin	Comment
1	Gross: atrophy Micro.: atrophy	Normal No info.	Normal Normal	Normal No info.	Normal Normal	1,920 gm. Centriobular fibrosis; fat moderate	490 gm. Hyperemia; fibrosis; "acute splenitis"	Spongy, red Erythroid hyperplasia	Normal Normal	No info.	No info.	Cause of death: appendicitis
2	Gross: flat, pale Micro.: within normal limits	Congestion Marked hemofuscinosis of muscularis propria	Congestion Mild hemofuscinosis	Enlarged Within normal limits	Normal Interlobular fibrosis, moderate	1,240 gm. Congestion	150 gm. (enlarged) Hyperemia; lining endothelial hyperplasia	Spongy, red Decided erythroid hyperplasia	Normal Normal	Normal Normal	Normal Iron free pigmentation, basal layer	Cause of death: multiple hemorrhages Deformed dwarf
3	Gross: normal	Normal, "velvety mucosa"	Normal	Enlarged	Normal	1,100 gm.	210 gm.	Spongy, red	Normal	Normal	Pigmentation; follicular hyperkeratosis Melanin	Cause of death: liver necrosis and multiple hemorrhages
4	Micro.: slight atrophy of pyloric mucosa Gross: atrophy	Villous clubbing with hyaline villous bands	Much mucus Normal	Chronic lymphadenitis Normal	Some atrophic	"Acute yellow atrophy"	"Acute splenitis"	Increased fat, paucity of megakaryocytes; erythroid activity good Normal	Normal	Congestion and hemorrhages Normal	Normal	Cause of death: natriotic thrombosis of dural sinus and cerebral veins
5	Micro.: atolysis, small myoma Gross: massive dilatation	Normal except for 2 serosal chondromas and some fibrous adhesions Massive dilatation; brownish pigmentation of the muscularis Hemofuscinosis of the muscularis propria atrophy of the muscularis	Normal Normal Normal except for brownish pigmentation of the muscularis Hemofuscinosis of the muscularis propria	Normal Normal Enlarged Unusual, disproportionate tuberculation	Fine fibrosis Normal	Extreme steatosis 1,875 gm. Congestion	Fibrosis; hemosiderosis 190 gm. "Acute splenitis"	Increased fat with pronounced erythroid activity Spongy, red Active and erythroid series	Normal Autolysis	Conspicuous connective tissue proliferation Normal	Pigmentation Melanin; hemosiderosis, slight	General atrophy of viscera except liver and pancreas Cause of death: volvulus of the sigmoid with resection, and acute purulent pyelonephritis Hemofuscinosis; old "neurodermatitis" and brawny edema of the legs

Gross: normal	Normal	Normal	Enlarged	Normal	1,580 gm.	300 gm.	Spongy, red	Normal	Normal	Cause of death: acute necrotizing laryngotracheitis (influenza virus B)
Micro.: normal	Increased leukocytes in lamina propria; occasional bizarre villous shapes	Endometriosiis, focal	Unusual, disproportionate trabeculation	Intraduobular fibrosis	Normal	Fibrosis and "acute splenitis"	Increased fat; increased erythroid activity	Autolysis	Status 1 yr. after drainage of left subphrenic abscess	
Gross: dilated; mucosa atrophic	Duodenum markedly dilated; superficial necrosis	Atrophic	Enlarged	Fibrotic	Normal	Normal	No info.	Normal	No info.	Cause of death: broncho pneumonia, emaciation.
Micro: mucosa atrophic	Superficial necrosis of duodenum and ileum	Atrophic	Hyperplastic lymphadenitis	No info.	Fatty degeneration	Acute splenitis	No info.	No info.	No info.	
Gross: mucosa flattened	Dilated	Volvulus of sigmoid; proctocolon dilated	No info.	Normal	1370 gm.	45 gm.	Normal	Normal	No info.	Cause of death: acute intestinal obstruction secondary to volvulus of sigmoid
Micro: no info.	Autolysis	No info.	Fibrous cords in sinusoids	No info.	Normal	Normal	No info.	No info.	No info.	
Gross: dilated; mucosa atrophic	Markedly dilated jejunum and ileum	Dilated; proximal to splenic flexure	Normal	Normal	1150 gm.	25 gm.	Normal	Normal	No info.	Cause of death: dilatation of intestine ? volvulus ? angulation
Micro: no info.	Normal	Normal	Accentuation of tissue system	No info.	Fatty change	Normal	No info.	No info.	No info.	
Gross: slightly dilated	Thin wall, atrophy of mucosa	Normal	Normal	Normal	800 gm.	82 gm.	Scanty	Normal	No info.	Cause of death: caechexia
Micro: no info.	Absence of villi and glands; vacuolar degeneration of musculature	Normal	No info.	No info.	Normal	Normal	No info.	No info.	No info.	
Gross thin wall; atrophy	Thin wall; ulcerations of small bowel; perforation of jejunum	Thin wall of descending and proximal transverse colon	Enlarged	80 gm.	2400 gm. friable	230 gm.	No info.	Cortex extremely thin	No info.	Cause of death: caechexia, gastrointestinal bleeding, pulmonary infarction
Micro: autolytic change	Atrophy, ulceration, cellular infiltration	Autolytic changes	Fibroid and fibrous tissue replacement	Normal	Congestion; heavy cellular infiltrate in periportal areas	Congestion	No info.	Congestion	No info.	

tients who were in clinical relapse at the time of their death one died of severe hemorrhagic manifestations and tetany (Case 2); one succumbed to volvulus of the sigmoid (Case 8); another to acute pyelonephritis following resection of the sigmoid for volvulus (Case 5); one died of ileus probably caused by angulation or volvulus of the splenic flexure; four patients died of extensive cachexia complicated in three by such conditions as marantic thrombosis of the dural sinus and cerebral veins (Case 4), confluent bronchopneumonia (Case 7), and gastrointestinal bleeding associated with prolonged steroid therapy (Case 11). The following is a summary of the findings in the organs (Table I).

Stomach. In seven of the cases the gastric mucosa was found to be grossly atrophic. This change was described on microscopic examination in four instances. In two patients extensive autolytic change prevented adequate description. Gross dilatation of the stomach was found in four instances. In Case 5, hemofuscinosis of the cytoplasm of the smooth muscle cells was present. In one patient there were numerous plasma cells and leukocytes in the lamina propria.

Small Intestine. In four instances the small intestine was found to be grossly normal. In two of these cases, microscopic examination was also normal. Atrophy and thinning of the wall was the outstanding change in the others (Fig. 1A). Gross dilation was described in three instances, two of which were associated with intestinal obstruction due to volvulus. Changes of the villi, consisting of flattening and thickening of the tips (clubbing), were specifically described in four cases (Fig. 1B, C). In other instances this change was apparently obscured or confused with post-mortem autolytic change. Moderate increase in the cellularity was frequently found. In one patient (originally described by Schein (5)) peculiar stromal hyaline band formations associated with marked deformation of the villi were found in all parts of the small intestine. In two cases large amounts of granular pigment, probably hemofuscin, were found in the muscularis (Fig. 2).

Large Intestine. The colon in the majority of instances was normal. The mucosa did not reveal the atrophic features found in the small bowel except in one case. Two of the patients died as a result of volvulus of the sigmoid. A third patient was believed to have died as the consequence of either a volvulus or an angulation of the splenic flexure. The marked dilatation of the colon in these patients might have been a predisposing factor in the development of the volvulus (15). An additional predisposing factor may have been the presence of a long mesentery. Minimal hemofuscinosis of the muscularis of the colon was seen in two instances.

Mesenteric Lymph Nodes. The mesenteric lymph nodes were enlarged in five cases. Many of these nodes revealed an unusual, disproportionate fibrous trabeculation. In three cases there was a chronic lymphadenitis. In Case 11 the lymphatic capillaries were markedly dilated and were surrounded by chronic inflammatory cells as well as an unusual variety of large cells resembling mast cells (Fig. 3).

Pancreas. The pancreas revealed various degrees of intralobular and interlobular fibrosis in four cases. These changes for the most part were not marked. In the remaining cases, the pancreas was grossly and microscopically normal.

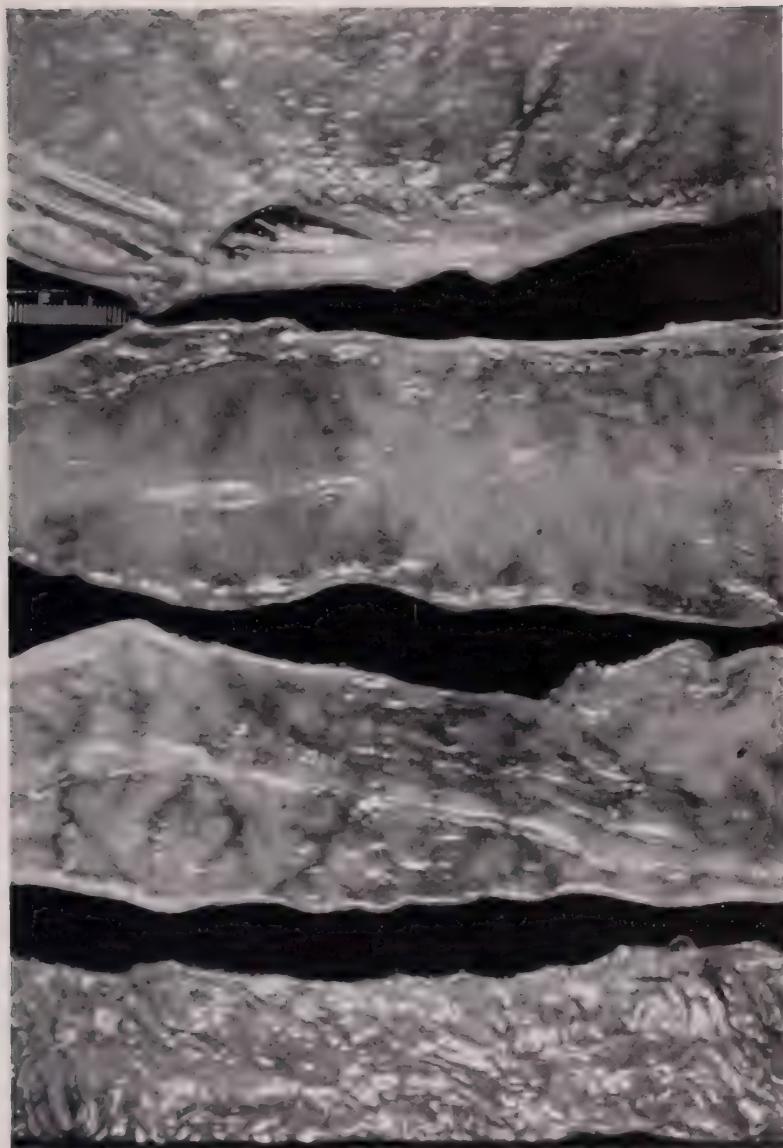


FIG. 1A. Diffuse atrophy and thinning of small bowel wall (Case 10, autopsy material).

There was no evidence of biliary disease. Some acinar atrophy as seen in hunger states was found in one case.

Liver. The liver varied in weight from 800 to 2400 gm. Several of the cases showed hepatomegaly of various degrees. Fatty changes, especially marked in Case 4, were seen in several instances, whereas others merely showed congestion. There was no uniform or characteristic appearance of the liver. In Case 3, an unexpected and severe acute yellow atrophy was found at autopsy examination. One case revealed centrilobular fibrosis. In Case 11, the liver was extremely

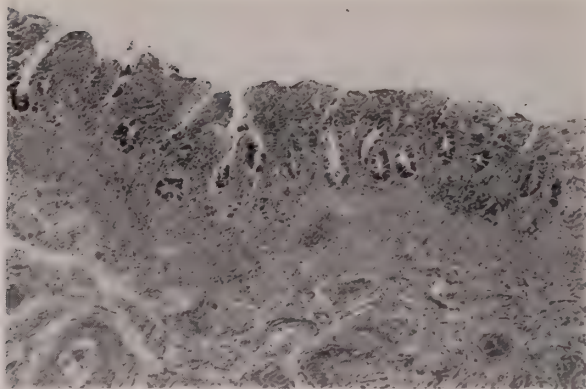


FIG. B

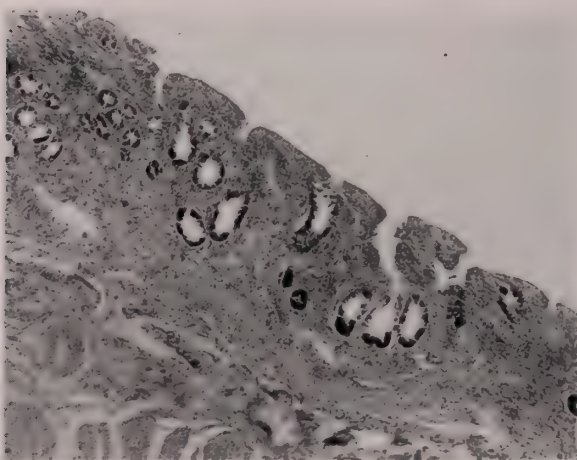


FIG. C

FIG. 1B & C. Flattening and thickening (clubbing) of villi as seen in autopsy cases.

friable and there was a heavy periportal leukocytic infiltration probably related to the patient's septic state.

Spleen. The spleen varied in weight from 45 to 410 gm. Five of the cases showed an acute "splenitis". There were varying degrees of congestion in several instances. Three cases revealed an unusual degree of fibrosis.

Bone Marrow. The bone marrow in four cases revealed erythroid hyperplasia associated with an otherwise hypoplastic marrow with increased amounts of fat.

Adrenals. The adrenals revealed no abnormal change except in Case 11, in which the cortex was unusually thin. This was the only patient of this series who had received prolonged steroid therapy.

Parathyroids. In the five cases in which the parathyroids were described, in only one instance was there any abnormality. In Case 4 there was a conspicuous connective tissue proliferation throughout the gland. Evidence of parathyroid hypertrophy was not seen.

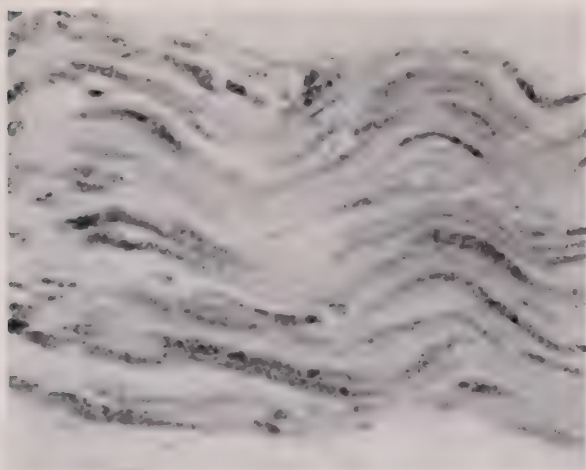


FIG. 2. Granular pigment in the muscularis (autopsy material).

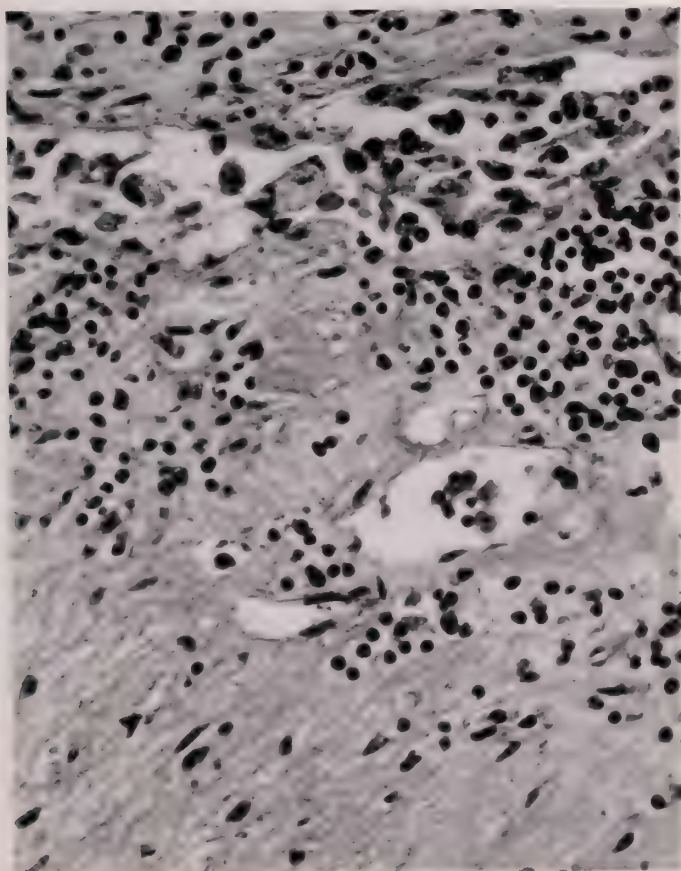


FIG. 3. Mesenteric lymph node (Case 11, autopsy material). Note dilatation of lymphatic capillaries surrounded by chronic inflammatory cells and replacement of lymphoid by fibrous tissue.

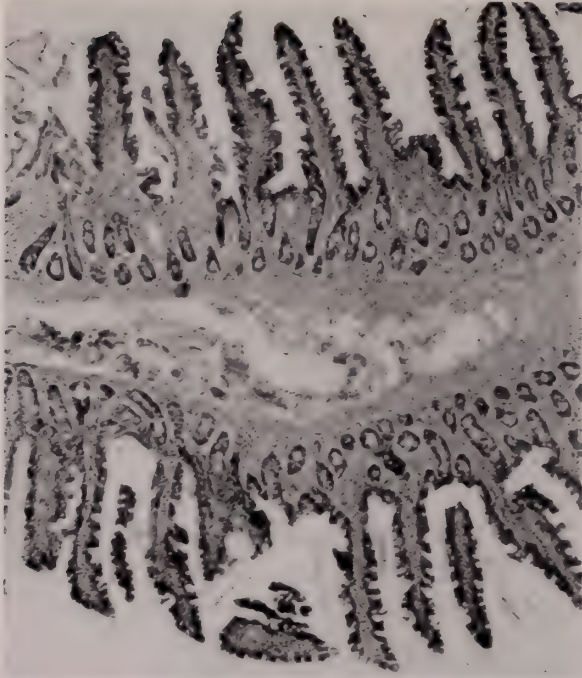


FIG. 4. Finger-like appearance of normal villi (Jejunal biopsy).

Skin. The skin was examined in five cases, three of which showed various degrees of pigmentation. There was an increase of iron-free pigmentation (melanin) in the basal layer.

STUDIES OF BIOPSY MATERIAL

Jejunal biopsies were performed in four patients with sprue, currently undergoing treatment with corticosteroids, by Dr. M. Shiner utilizing her modification of the Wood biopsy instrument (13). In addition, two patients, of whom one had clinical malabsorption other than sprue (pancreatic insufficiency secondary to carcinoma), and the other pernicious anemia, were studied. In the latter two cases the jejunal mucosa was normal. In the sprue patients the changes were striking. The villi, instead of having the normal narrow finger-like configuration (Fig. 4), were markedly thickened and flattened, with considerable loss of villous surface area (Fig. 5). The surface epithelium covering the villi assumed a cuboidal shape rather than the usual columnar type of epithelium. The striated border, however, was well preserved. The nuclei were irregular in shape and position within the cells. There appeared to be an increase in the number of goblet cells. In the lamina propria there was slightly more than the average cellular infiltration consisting mainly of lymphocytes, plasma cells and occasionally eosinophils.

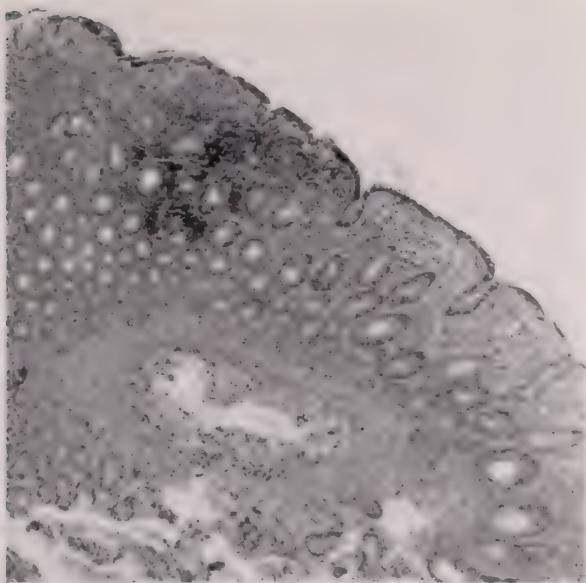


FIG. 5. Marked thickening and flattening of villi with considerable loss of absorbing surface area (Jejunal biopsy). Patient received prolonged steroid therapy.

A more detailed analysis of the biopsy findings is presented elsewhere in this symposium (14).

DISCUSSION

In the post-mortem examinations no characteristic or uniform pattern of pathological aberration is apparent. The logical assumption, based on clinical evidence that the malabsorption syndrome in sprue is due to a derangement or defect in the small bowel, is not conclusively supported by evidence obtained from autopsy material. Since a number of the autopsied cases and all of the biopsied cases revealed some change in small bowel morphology, it would appear that this change is causally related to the clinical picture. The marked atrophy of the small intestinal mucosa and the blunting and thickening of the villi seen in many of the cases obviously lessen the surface area available for absorption. It might of course be argued that those changes in the mucosa are the result of alterations in small bowel motility, stasis, changes in intestinal flora, absorption of toxic products or lack of specific nutritional factors, such as are seen in pernicious anemia where gastric mucosal atrophy is believed to result from a prolonged deficit of vitamin B₁₂-intrinsic factor. In many instances, post-mortem autolytic change has been so extensive as to prevent interpretation of the findings. The large bowel does not appear to participate in this process to any great extent.

It would appear that study of material obtained by jejunal biopsies in living patients would permit a more exact interpretation of any pathological change by eliminating the factors of agonal and post-mortem autolysis seen in many

autopsied cases. The normal mucosa obtained by the oral biopsy technique reveals thin finger-like villi. The jejunal villi of sprue patients are thick and blunt. The area available for absorption from the lumen is markedly diminished. The degenerative changes seen in the surface epithelium may likewise contribute to the absorption defect. The apparent increase in the goblet cells suggests hypersecretion of mucus, possibly as a response to irritation. It is significant that one patient who had pancreatic insufficiency secondary to carcinoma and was markedly cachectic had a normal jejunal mucosa. The oral technique of obtaining biopsy material is a significant contribution to the study of small intestinal disease.

The significance of pigmentation observed in the small intestine in some of the cases is not clear. Pappenheim and Victor (16) have described the presence of "ceroid" pigment in animals deficient in vitamin E and in man with malabsorption syndrome. In the latter category it is believed that vitamin E deficiency is part of the overall deficiency of fat-soluble vitamins (vitamin A, chemical and clinical evidence; vitamin K; hypoprothrombinemia; vitamin D, abnormalities of calcium metabolism).

It is not clear what the changes in the mesenteric lymph nodes signify. Are the evidences of chronic lymphadenitis and fibrosis primary, producing blockage of the lymphatic channels and hence diminished absorption? In only one instance was there evidence, in the form of distended mesenteric lymphatic capillaries, that this explanation is feasible. It is more likely that the changes are secondary to a chronic degenerative process in the bowel.

Interpretation of the significance of the varying degrees of fibrosis of the pancreas is obscure. It is perhaps related to the severe nutritional deficiency (17). Because this change was not observed in many of the cases, there probably is no pathogenetic significance which can be ascribed to these findings.

Similar conclusions may be drawn for the role of the liver in sprue. The most consistent, but not invariable, finding was some degree of fatty change resulting probably from the nutritional defects in these patients. Similarly, the instance of acute yellow atrophy probably represents an unusual complication in a malnourished individual. Sepsis and malnutrition may prove responsible for friability and increased cellular infiltration observed in Case 11.

There were no changes in the spleen considered to be of significance.

Although both the adrenal (18) and parathyroid (19) glands have been reported as being implicated in the cause of sprue, there was no evidence in the present study to substantiate these contentions. Atrophy of the adrenals, noted in Case 11, was believed to have been secondary to the prolonged use of steroid hormones. The connective tissue proliferation of the parathyroids noted in Case 4 cannot be explained. In no instance was there evidence of hyperparathyroidism as might be expected in patients with long standing steatorrhea.

Erythroid hyperplasia of the bone marrow, which was present in several cases, is a non-specific finding frequently seen in anemic states. The absence of megaloblastic patterns at autopsy is due to preceding therapy with liver extract and/or vitamin B₁₂. The previously described changes in osteomalacia could not be

confirmed since no osseous tissue was removed for examination in any of the cases.

The skin pigmentation in the few cases in which it was described was due to an increase in the melanin content in the basal layers. Hemofuscin has not been found in any case.

It may be concluded from these studies that the major and significant pathologic aberrations are to be found in the small intestine. Although it is conceivable that the absorptive defect may result solely from these physical and morphological changes, it is also possible that the changes are secondary to some other defect which results in mucosal atrophy, much as prolonged vitamin B₁₂-intrinsic factor insufficiency results in gastric atrophy in patients with pernicious anemia (20).

It is conceivable that the basic defect of absorption in sprue is caused by an alteration in genetically controlled enzymatic mechanisms in the intestinal mucosa and that morphologic changes are secondary to this disturbance. Studies of enzymatic activity of small intestinal mucosa obtained by biopsy would undoubtedly be fruitful. Similar studies evaluating the role of steroid hormones would likewise be of great value in the study of this baffling disorder.

SUMMARY

Eleven post-mortem examinations on patients with idiopathic sprue were performed. In addition, jejunal mucosal biopsies were done in four living sprue patients. In all patients in the latter category and in many of the autopsied cases there was marked atrophy of the small intestinal mucosa with morphological changes in the villi which appreciably diminished the area available for absorption. No other organ system appeared to be involved to the extent that it might be considered to play a primary role in this disorder.

It is concluded that the major pathological alterations in sprue are to be found in the small intestine. It is not clear however whether these changes are due to a specific local enzymatic or nutritional defect or whether they result from toxic degeneration or other influences. The use of the small intestinal biopsy technique is considered to be a useful method of studying intestinal malabsorption. It would be especially valuable in the evaluation of milder disturbances of absorption in children and adults.

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SMALL INTESTINAL BIOPSIES BY THE ORAL ROUTE

Histopathologic Changes in the Malabsorption Syndrome

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The method of taking duodenal and jejunal biopsies by the blind suction technique can be used in out-patients as well as in-patients. It requires no special preparation.

INSTRUMENT AND TECHNIQUE

The small intestinal biopsy tube (Fig. 1) is a flexible plastic tube 161.5 cm. long and 5 mm. in diameter. The headpiece is 2.5 cm. long and has a diameter of 1.3 cm. at its widest point. The diameter of the biopsy hole is 3.5 mm. The knife cylinder is 9 mm. long and is rigid at the distal end. An airhole is situated in one of its ridges extending down the side of the knife cylinder, thus allowing air to reach the rubber balloon at the distal end of the headpiece. The tailpiece of the instrument contains the other end of the wire which runs along the whole length of the tube to be screwed into the knife cylinder. Attached to the tailpiece is a lateral exhaust to which a manometer and syringe can be attached to provide negative pressure of known amount.

The fasting patient gargles with 2 to 3 ml. of a 1 per cent amethocaine (pontocaine) solution. He is placed on a fluoroscopic screening couch and, lying on his left side, the headpiece of the tube is gently guided to the back of the throat by the operator's two fingers. The patient is asked to swallow and the tube is easily pushed down. Once the stomach is reached, the progress of the headpiece is controlled by fluoroscopy. It is also aided by exerting pressure on the patient's abdomen to swing the headend of the instrument towards the pylorus (Fig. 2). An upright fluorescent screen may also be used, although manual palpation on the patient's abdomen is then somewhat less effective. The patient is then turned on to his right side and instructed to push the tube gently and very slowly into his mouth. Screening is resumed from time to time to watch the progress of the tube. As a rule the balloon is inflated when the headpiece has reached the duodenum, but sometimes the headpiece may pass the pylorus more easily if the balloon is blown up in the stomach. Sterile saline is the most effective way of inflating the balloon. The amount necessary to distend it should be established before introducing the tube. This quantity of saline is then injected through the lateral exhaust with a syringe. When the first or second part of the duodenum is reached (Fig. 3), duodenal biopsy may be taken. The headpiece of the biopsy tube can be carried further into the jejunum up to 20 cm. from the ligament of Treitz (Fig. 4). Owing to limitation in time and facilities of screening no distal parts of the jejunum were entered. But this should be possible in the future and, at least in certain patients, biopsies of distal parts of the jejunum should become available. The shortest time in which the duodenum or jejunum was reached was just under one hour. The average time was $1\frac{1}{2}$ to 2 hours.

Before biopsy is taken the balloon must be deflated using the syringe at the tail-piece. The manometer is then attached between the lateral exhaust tube and the syringe. The opening of the aperture of the headpiece is achieved by a downward movement of the rod of the tailpiece. Once a slight resistance is felt to downward movement of the rod, the rod is arrested, because further pressure will only result in coiling of the wire inside the flexible tube. Suction is then applied to the syringe to produce a negative pressure of 3 to 5 inches Hg on the manometer. It is dangerous to exceed a pressure of 10 inches Hg. Negative pressure is maintained while the tailpiece rod is pulled upwards by a sharp movement closing the aperture and securing the specimen which consists of a superficial piece of the mucosa

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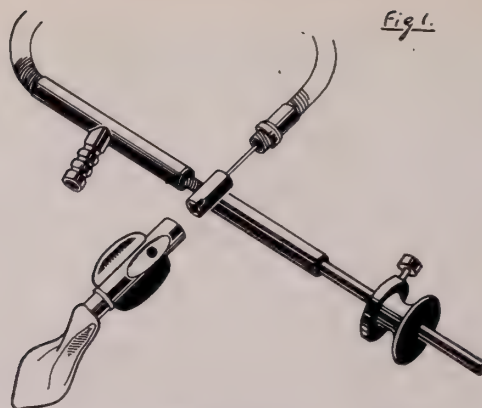


Fig. 1.

Jejunal-biopsy tube

P.G.M.S. 121.

FIG. 1: The jejunal biopsy tube.

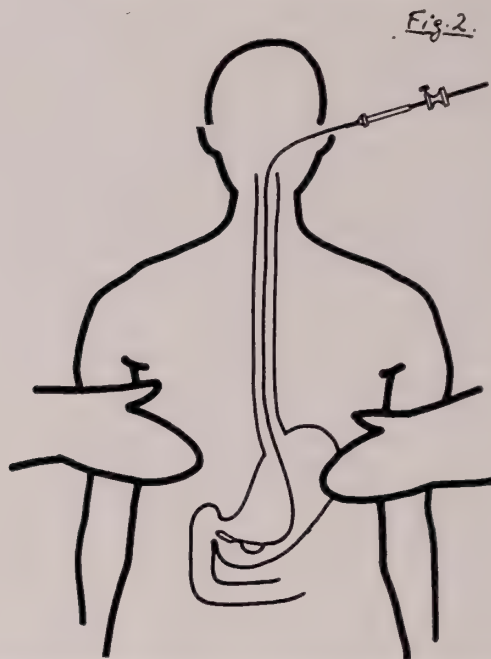


Fig. 2.

FIG. 2: Tube in stomach with operator's hands on patient's abdomen.

within the headpiece. The syringe is disconnected, air is released and the manoeuvre may be repeated. A sort of cutting sensation is transmitted to the operator's hand during the closure of the aperture. To withdraw the tube the patient is turned on his left side, avoiding pressure or traction on the tube during the upward pull. One or more specimens are usually found in the knife blade, or in the flexible part of the tube. These should be blown out gently with the syringe and immediately placed in a 10 to 15 per cent solution of formol in saline and two hours later in formol-saline sublimate for a further 24 hours. The usual histologic procedures are employed. It is important to fix the specimens as soon as possible to prevent autolysis. The patient is instructed to rest for two hours after the procedure. Any food is then allowed.

Fig. 3.

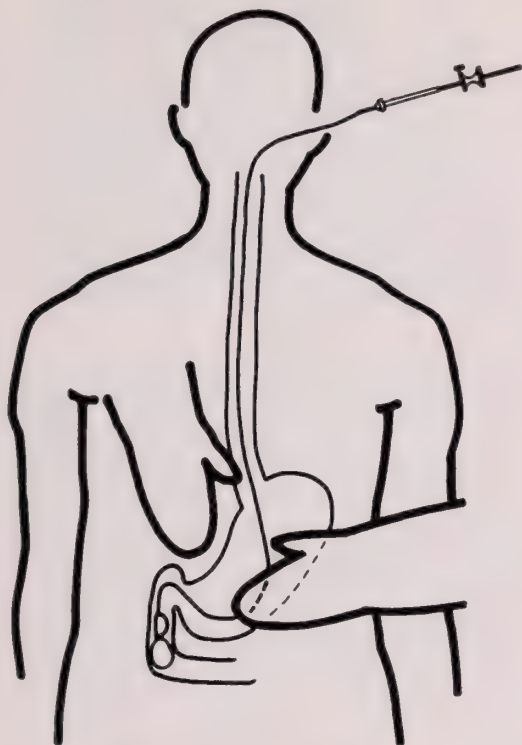


FIG. 3: Tube in duodenum.

Up to date 89 successful small intestinal biopsies have been taken without a single complication. The method may be therefore considered safe, providing reasonable care is exercised. The failure rate is estimated at roughly 1 in 4 biopsies. Failure is due to: 1) Inability to introduce the headpiece beyond the hypopharynx. This is rare; 2) Inability to pass the instrument beyond the pylorus. This still remains one of the most troublesome difficulties encountered; 3) Autolysis of the specimen. This is likely to follow too long a delay in withdrawing the tube, especially in the presence of plentiful intestinal juice inside the biopsy tube.

HISTOLOGIC FINDINGS IN CONTROLS

The specimens obtained varied both in number and size. From one to eight specimens were taken from a single patient. These had a length of 1 mm. to 1 cm., with an average of 3 to 4 mm., and included full thickness mucosa, muscularis mucosae and a thin layer of submucosa. Excellent preservation of the mucosal villi were seen in most specimens (Fig. 5). These are long, wavy, finger-like, slender projections lined by very regular columnar epithelium containing elongated nuclei situated towards the base of the cells. The rest of the cells are filled with a homogeneous material staining pink in the hematoxylin-eosin preparations. Mitosis is not seen in the nuclei of the villous epithelium. A well defined

Fig. 4.

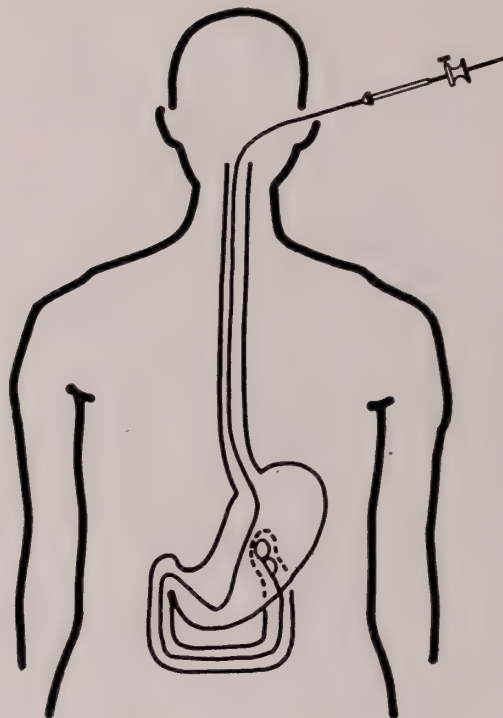


FIG. 4: Tube in proximal part of jejunum.

basement membrane lines their undersurface and a brush border can be seen clearly at their free surface. Goblet cells are scattered among the covering epithelium. In the glandular layer of the mucosa (Fig. 6) the villous epithelium forms the crypts and glands of Lieberkuhn. These are composed of columnar cells, somewhat shorter than those of the villi and containing ovoid nuclei. Mitosis is conspicuous within the nuclei of the glandular epithelium. The appearances of active mitosis of the cells of glands and crypts of Lieberkuhn and their absence in the villous epithelium lend support to the observations made by Vitale et al, Grampa and Dustin, and Le Blond and Stevens, that the former cells are precursors of the latter (villous) cells (1-3). Goblet cells are more numerous in the glands of Lieberkuhn, and Paneth and argentaffin cells can be clearly seen within the glands in hematoxylin-eosin preparations. The interstitial connective tissue contains plasma cells, lymphocytes, histiocytes, eosinophils and occasional mast cells and neutrophil polymorphs. The more detailed histology of the small intestinal mucosa and variations from the normal have been described by Doniach and Shiner (4).

HISTOPATHOLOGIC FINDINGS IN THE MALABSORPTION SYNDROME

The controversy over histologic changes in the small intestines in sprue has been raging for more than half a century. The difficulties were accentuated by

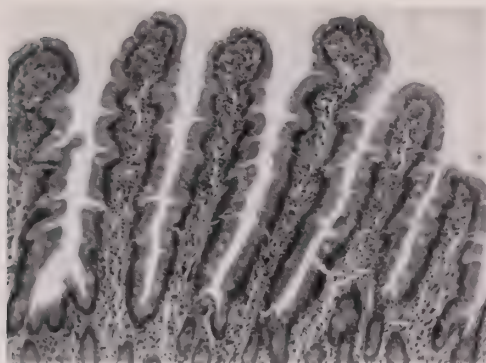


FIG. 5: Normal jejunal villi. H. & E. $\times 175$.

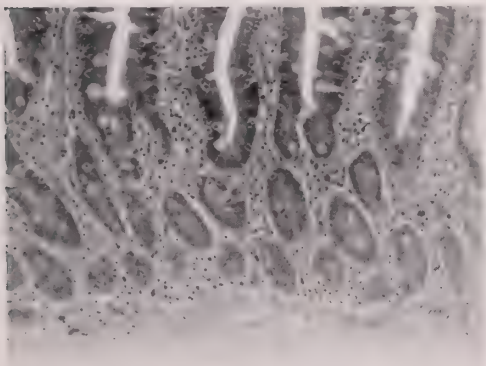


FIG. 6: Glandular layer of jejunal mucosa, showing normal glands of Lieberkuhn. H. & E. $\times 235$.

the fact that as so few cases came to laparotomy, the evidence for pathological changes in the gut had to be obtained from the post-mortem room and, due to the rapid setting in of autolysis, the small intestine is notoriously difficult to study after death. Thus Wethered, who found atrophy of the small intestine in sprue, expressed considerable doubt as to the validity of his post-mortem findings (5). On the other hand, Thaysen, in 1931 and 1934, could find no evidence of any histologic changes attributable to sprue and his views have become accepted up to this present day (6). Various workers, notably Manson-Bahr, found ulceration in the small intestine (7). Others, like Mackie and Fairley, considered that there were degenerative, non-inflammatory changes in the villi leading eventually to shrunken and acellular villi and degeneration of the glands of Lieberkuhn with thinning of the wall of the small intestine (8). Mucosal and submucosal round cell infiltration of the small intestine were found in other cases (9). Schein in 1947 described a post-mortem case of idiopathic, non-tropical sprue in which he found clubbing and mushrooming of the small intestinal villi in the tip of which hyaline material was deposited (10).

Adlersberg and Schein in their study of six autopsied cases of idiopathic sprue observed that several anatomic findings, while not necessarily characteristic or pathogenetically significant, were encountered at autopsy in cases of sprue (11).

Atrophy of the small intestinal mucosa and villous deformities consisting of flattening and blunting of the villi (clubbing) as well as increased cellularity of the lamina propria were noted. They described instances of hemofuscinosis of the muscularis of the gastrointestinal tract, chronic mesenteric lymphadenitis with replacement of lymphatic tissue by hyaline and fibrous bands, centrolobular fibrosis of the liver and various degrees of pancreatic fibrosis (in the absence of biliary disease). Although it is apparent that these changes in the bowel and mesenteric lymph nodes are such as to impair absorption the more fundamental pathogenetic implications were not clear.

In 1949, Paulley obtained biopsy specimens by laparotomy of 3 cases of idiopathic, non-tropical sprue and came to the conclusion that the absorptive defect was due to flattening of the villi and infiltration of the mucosa and submucosa with chronic inflammatory cells. He described a picture of non-specific jejunitis (12).

Many theories have been put forward as to the reason for the possible defect in absorption in the sprue syndrome, none of them satisfactory. Thus bacterial invasion, edema, circulatory changes and allergy have all been suggested. With the method of obtaining small intestinal biopsies by the oral route, it is hoped that many doubts as to the underlying histopathologic defect in sprue will be cleared up. From the study of the histology of the mucosa of the upper small intestine in 17 cases of sprue which, with the exception of one case, was obtained by the biopsy tube method, a few findings are summarized:

1. Histologic changes in the small intestine in sprue occur in some cases but not in all.
2. These changes are non-specific and consist of mucosal, chiefly villous atrophy. With the exception of one case of pernicious anemia, which has not been further investigated, mucosal atrophy has so far been observed only in sprue and not in 12 small intestinal biopsies obtained from patients with small and large intestinal tract disease and 15 control cases. The former group consisted of four patients with ulcerative colitis, two with regional ileitis, five with non-specific diarrhea and one with post-gastrectomy [dumping] syndrome. The latter group consisted of four patients with x-ray negative dyspepsia, six with gastric ulcer, two with cirrhosis of the liver, one with congenital hemorrhagic telangiectasis, one with paroxysmal nocturnal hemoglobinuria and one with "posthepatitis syndrome".
3. Histologic changes in the small intestine were seen mainly in idiopathic non-tropical sprue, tropical sprue and a possible case of celiac disease.
4. A repeat biopsy on one case of idiopathic, non-tropical sprue showing abnormal mucosa was carried out and revealed identical mucosal changes. This suggests that the disease process must affect a considerable portion of the upper small intestinal mucosa and that, although the patient was in clinical remission and under treatment with folic acid at the time the second biopsy was taken, the histopathologic pattern remained unchanged.
5. Another case of idiopathic, non-tropical sprue who came to laparotomy shortly after small intestinal biopsy by the oral route was performed had

TABLE I
Varieties of steatorrhea and degree of involvement of small intestinal mucosa

Idiopathic Non-Tropical	Histology	Tropical	Histology	Pancreatic	Histology	Post-Gastrectomy	Histology	Miscellaneous	Histology
Case 1	Severe atro- phy Partial	Case 10	Severe atro- phy	Case 17	Normal	Case 14	Normal	Case 11—post- gastrect., but probably idi- opathic	Severe atro- phy
2	Partial atro- phy					15	Normal		
3	Partial atro- phy					16	Normal	Case 12—see secondary to tuberculosis? idiopathic?	Partial atro- phy
4	Severe atro- phy							Case 13—see secondary to chylous ob- struction	Partial atro- phy
5	Severe atro- phy								
6	Severe atro- phy								
7	Severe atro- phy								
8	Severe atro- phy								
9	Severe atro- phy								

TABLE II

Clinical data of 17 patients with steatorrhea and the degree of involvement of small intestinal mucosa

Case	Sex	Age	Duration of symptom in years	Etiology	Diarrhea	Wt. Loss	Hb. %	FF	PP	GTT	Small Bowel Study	Bone Marrow	Histology
1. A. C.	F	61	1½	Idiopathic	Gross	28 lbs.	76%	14	—	Normal	Clumping	Megalo-blastic	Severe atrophy
2. J. M.	M	62	2	Idiopathic	None	Slight	43%	47.6	—	—	Normal	Megalo-blastic	Partial atrophy
3. E. B.	F	64	3	Idiopathic	None	Moderate	72%	34	—	Flat	Normal	Normal	Partial atrophy
4. L. B.	M	25	20	Idiopathic	Moderate	50 lbs.	90%	Slight increase in	5.6	Flat	Clumping	—	Severe atrophy
5. N. F.*	M	46	14	Idiopathic	Gross	Gross	36%	Gross increase in	—	Flat	Clumping	—	Severe atrophy
6. P. S.*	M	58	25	Idiopathic	Gross	40 lbs.	80%	62.4	7.0	Flat	Clumping	—	Severe atrophy
7. S. H.*	F	72	21	Idiopathic	Gross	39 lbs.	32%	56.5	3.6	Flat	Clumping	Normal	Severe atrophy
8. C. N.*	F	46	45	Idiopathic	Gross	38 lbs.	86%	Gross increase in	5.6	Flat	Clumping	—	Severe atrophy
9. L. W.	F	15	2	Idiopathic	Mild	33 lbs.	22%	8.6	4.3	Flat	Clumping	Megalo-blastic	Severe atrophy

	F	54	3 ₁	Tropical sprue	Gross	10 lbs.	68%	16.2	5.4g	Flat	C'lump- ing	Megalo- blastic	Severe atro- phy
10. R. W.													
11. J. J.	M	65	1	Idiopathic ? Post-gas- trectomy	Gross	27 lbs.	68%	46.8	4.7		C'lump- ing	Megalo- blastic	Severe atro- phy
12. H. W.	M	55	1 ₂	? Secondary ? Idiopathic	Gross	30 lbs.	70%	27			C'lump- ing, dis- tension	Macronor- moblas- tic	Partial atro- phy
13. G. E.	M	42	10	Secondary, chylous ob- struction	Mod- erate	None	60%	7.7	6.0	Normal	Normal	Normal	Normal
14. R. P.	M	50	8	Post-gastrec- tomy	Mod- erate	Mod- erate	92%	10.7			Rapid emp- tying C'lump- ing		Normal
15. S. F.	M	51	1	? Post-gas- trectomy	Gross	42 lbs.	95%	30	4.0				? Nor- mal
16. G. A.	M	56	1 ₃	Idiopathic Post-gastrec- trectomy	None	?	33%	47.6			Normal	Megalo- blastic, iron def.	Normal
17. M. V.	F	63	7 ₁₂	Pancreatic steatorrhea	Mod- erate	39 lbs.	76%	Sudan III posi- tive	5.6	Diabe- tic	Normal	Iron def.	Normal

FF = Fecal fat expressed as percentage of dry fecal weight.

PP = plasma proteins in gm./100 ml. of serum.

GTT = glucose tolerance test curve.

* Therapy resistant; prolonged steroid therapy resulted in subsidence of diarrhea, improvement of steatorrhea and considerable weight gain.

two biopsies taken from the terminal ileum. These showed changes of mucosal atrophy similar to those seen in the upper small intestine.

6. Four cases studied at The Mount Sinai Hospital in New York were controlled on steroid therapy, prior to being subjected to biopsy by the oral route. These four patients showed the severest pathologic changes of the mucosa, indicating that, despite marked clinical improvement after administration of steroids, improvement from the histopathologic point of view is not seen.

Table I shows the various types of malabsorption syndrome into which the 17 patients so far studied fell and the degree of mucosal changes. It will be seen that gross mucosal changes, with the possible exception of one case, were seen only in the idiopathic, non-tropical sprue and in tropical sprue. These cases comprised a total of 10 patients. In the post-gastrectomy (3 patients) and pancreatic (1 patient) types of steatorrhea the small intestinal mucosa was found normal. One case of steatorrhea secondary to chylous obstruction likewise showed no abnormal mucosal changes. But two other patients (of whom one may be considered a case of steatorrhea secondary to tuberculous enteritis, and the other a possible case of post-gastrectomy steatorrhea, although there was

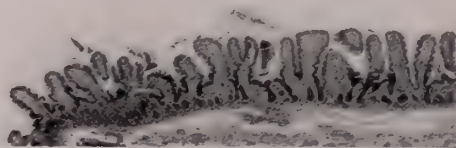


FIG. 7: The jejunal villi in non-tropical sprue, showing clubbing and mushrooming. H. & E. $\times 55$.

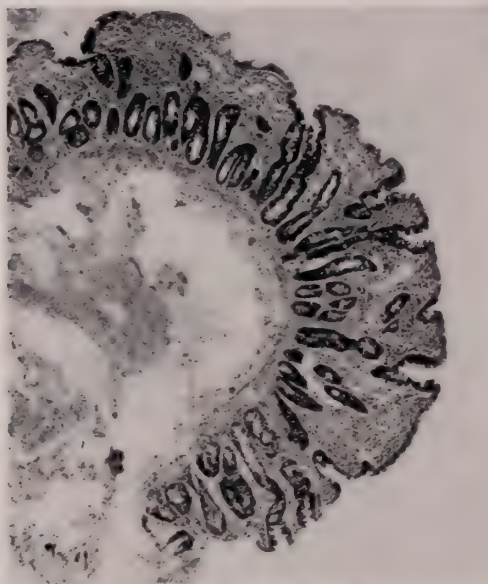


FIG. 8: The jejunal villi in non-tropical sprue showing almost total flattening. H. & E. $\times 55$.

evidence that steatorrhea might have been present before gastrectomy) showed mucosal atrophy, which was more severe in the second.

Mucosal changes varied from partial atrophy, in which the main abnormalities observed consisted of blunting and reduction in the size of the villi and therefore a total reduction of villous surface area, to gross and severe atrophy in which the villi were almost totally flattened and the cells of the surface epithelium and crypts and glands of Lieberkuhn showed atrophic changes.

Villi. Changes from clubbing and mushrooming (Fig. 7) to almost total flattening (Fig. 8) were observed. There was considerable variation in size and shape of villi within the same biopsy in the milder cases, but in the severe cases a uniform flattening and almost total obliteration of villi was seen. The surface epithelium covering the villi showed striking changes which were mainly confined to the severely atrophic mucosa. Instead of the regular, tall, columnar type of cells with elongated, dark staining nuclei situated more basally and a pink staining homogeneous cytoplasm, the cells were reduced in size to low columnar cells with small irregular nuclei and vacuolated cytoplasm. The basement membrane appeared interrupted or totally absent, but the brush border seemed always intact (Fig. 9). Goblet cells were more numerous in the villi in some biopsies but this was not a universal picture. The villous stroma showed no striking abnormalities apart from edema and congestion in some biopsies and moderate increase in cellular infiltration, consisting mainly of lymphocytes, plasma cells, eosinophils and occasionally polymorph neutrophils, in others. The flattening of villi, accentuated by the edema observed in some biopsies, imparted an impression of increase in thickness of the lamina propria of the glandular layer of the mucosa.

Crypts and glands of Lieberkuhn. Gaping crypts and distended glands were seen in many specimens though not in all (Fig. 10). In these the epithelium was flattened and the nuclei were irregular in size. In some cases mitosis was reduced. Goblet cells were numerous in some specimens where they contained deep blue-staining material in hematoxylin-eosin preparations. It must be pointed out that normal variation of the glandular epithelium is so common that, although it was more frequently seen in atrophic mucosa, it was difficult to correlate glandular abnormalities with overlying cellular atrophy in the villi. Cellular infiltration of

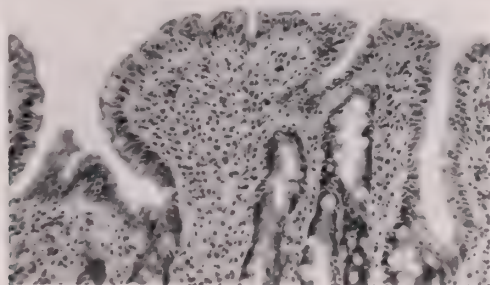


FIG. 9: High power view of clubbed villi showing irregular nuclei and vacuolated cytoplasm of surface epithelium. The basement membrane seems interrupted in places but the brush border is well preserved. H. & E. $\times 300$.

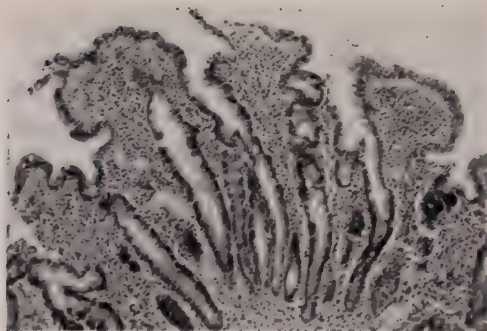


FIG. 10: Jejunal mucosa in tropical sprue showing gaping and distended glands of Lieberkuhn with flattened epithelium and irregular nuclei, also some increase in goblet cells. H. & E. $\times 300$.

the glandular layer was increased in some specimens and was of the same variety as in the villi.

DISCUSSION

Evidence has been presented that mucosal, though mainly villous, atrophy of the small intestine is a feature of idiopathic sprue and has been found in all cases of idiopathic non-tropical sprue, in one case of tropical sprue and in a possible case of celiac disease. As yet the number of cases with secondary varieties of sprue which were biopsied is too small to allow us to state that no abnormal mucosal changes are seen here. It is at times extremely difficult if not impossible to differentiate between a secondary type of sprue and a latent primary sprue reactivated by intestinal disease or alteration in the intestinal mechanics. It is conceivable that mucosal atrophy is not a uniform process along the whole of the small intestine or that it varies in degree from site to site. This was emphasized by Paulley who found patchy atrophy of the small intestinal mucosa post-mortem in a case of seemingly idiopathic, non-tropical sprue who had also had a partial gastrectomy with exacerbation of his steatorrhea (13). Jejunal biopsy carried out one year after partial gastrectomy showed normal mucosa.

The etiology of idiopathic sprue still remains obscure. Most observers class celiac disease, idiopathic non-tropical sprue and tropical sprue as one and the same disease occurring at different phases of life and requiring certain trigger mechanisms for its activation (14). The absorptive defect is considered due to congenital and hereditary abnormalities. This theory seems to be widely accepted on the grounds that celiac disease occurs in families and that many celiac children, after variable periods of remission, develop the adult type of sprue (15). Case 9 is the youngest case of "idiopathic sprue" in this series, and Cases 4 and 8 gave a clear history of celiac disease in childhood. Yet the histopathologic changes in these patients differed in no way from those found in patients with idiopathic, non-tropical sprue in whom no history of celiac disease was obtainable. Accepting the common histologic bond between celiac disease, adult idiopathic non-tropical sprue and tropical sprue, one might postulate that the congenital and hereditary defect consists perhaps in primary atrophy of the small intestinal mucosa or some underlying mucosal defect which eventually leads to

secondary atrophy. Final proof might be obtained when small intestinal biopsies are taken in children with celiac disease. An interesting finding is the discrepancy between villous and glandular atrophy in the biopsies of patients on steroids as compared with the uniform atrophy affecting both villi and glands in those cases not receiving steroids. It is possible that hormone therapy influences cellular regeneration in some way thereby improving absorption at least to some extent.

SUMMARY

A method of taking small intestinal biopsies has been described and the histopathologic changes affecting the small intestinal mucosa in 12 patients with the malabsorption syndrome have been demonstrated.

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CLINICAL ASPECTS OF THE MALABSORPTION SYNDROME (IDIOPATHIC SPRUE)

OBSERVATIONS IN 94 PATIENTS

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In the broader concept of today, the malabsorption syndrome (idiopathic sprue) is a genetically transmitted complex metabolic disorder (1). The defect of absorption represents the main clinical abnormality; however, sprue is more than defective intestinal absorption. It may start early in life or remain latent for many years and become manifest during adult life. It appears now that celiac disease in children, as well as tropical and non-tropical sprue and idiopathic steatorrhea in adults, are clinical manifestations of the same basic metabolic disturbance, chiefly characterized by impaired intestinal absorption (2-5). Many environmental factors such as the stress of tropical climates, tropical and non-tropical infections, malnutrition, underweight, certain medicaments (antibiotics) and perhaps psychological disturbances are precipitating or "triggering" mechanisms converting a predisposed person with "latent sprue" into a patient with symptoms and signs of "manifest sprue" (6).

In idiopathic (primary) sprue there are no specific gross changes in the gastrointestinal tract although some abnormalities have been observed in advanced instances of this disorder in post-mortem studies and in biopsies. In contrast, secondary sprue, which may simulate the idiopathic form in its clinical manifestations, is caused by severe gross disease of the small bowel such as lymphosarcoma, amyloidosis, intestinal lipodystrophy (Whipple's disease) and certain forms of jejuno-ileitis. Malabsorption syndromes resulting from extensive resection of the small bowel, a gastro-jejuno-colic fistula, or inadvertent gastro-ileostomy following subtotal gastrectomy, as well as steatorrhea due to pancreatic disease or resection, must be also differentiated from idiopathic sprue (7, 8).

The present study is a review of 94 patients with idiopathic sprue observed at The Mount Sinai Hospital from 1931 to 1956. The patients all had primary sprue established by clinical and laboratory evidence. They revealed at some time all or most of the typical features of this syndrome as described later. They had no roentgenologic or other evidence of *gross* organic disease in the gastrointestinal tract. They have been selected for this study from a larger group of patients because of prolonged observation (average follow-up period over five years).

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GENERAL CONSIDERATIONS

The group included 32 men and 62 women. The predominance of women in the present series was also observed in the earlier report from this hospital (7). This has not been noted in most other reviews where the sex incidence was approximately equal (4, 9, 10). Manson-Bahr (11) noted a slightly larger number of women with tropical sprue.

The age at time of first observation ranged from 16 to 73 years with a mean of 45 years. The average age of the patients was the same in men and women (Table I). This is in agreement with observations published from England concerning idiopathic steatorrhea (4). Sprue has been observed at all ages with the usual median at about age 40 years (4, 5, 7, 12). Eight men and 15 women were Puerto Ricans who had lived for varying periods of time in New York.

The duration of symptoms when first seen ranged from one month to 52 years with a mean duration of 7.2 years. The long duration of symptoms prior to hospitalization has been noted by previous reviewers (13-15). The insidious onset of the disorder, the vagueness of symptoms and the tendency to spontaneous remissions led to delay in seeking medical aid and postponement of proper diagnosis. The duration of subsequent observation ranged from a single hospitalization (12 patients) to 22 years, with a mean follow-up period on 82 patients of 5.2 years.

Nineteen patients died, five men and 14 women, with an over-all mortality of 20.2 per cent (15.6 per cent in men, 22.6 per cent in women). Six patients died of progressive cachexia, in one instance terminating in thromboses of the dural sinuses and cerebral veins after an episode of severe tetany. In three patient respiratory infections were the immediate cause of death; acute necrotizing laryngotracheitis led to death in one and bronchopneumonia in two. In two patients severe bleeding was the immediate cause of death, associated with acute yellow atrophy of the liver in one. In two patients acute intestinal obstruction due to volvulus of the sigmoid was observed. This was the cause of death in one patient, while the other succumbed to acute pyelonephritis following resection of the sigmoid. Two patients with long-standing sprue succumbed to gastric carcinoma. One patient died of superimposed hepatic insufficiency. One patient died after an appendectomy for acute appendicitis. One patient at death had extensive ulceration of the small intestine. One patient (sprue in remission) died in an old age home of heart failure. Post-mortem examinations were performed in 14 patients. Eleven of these will be presented in detail elsewhere in this symposium (16).

TABLE I
Age of patients when first seen

Age (Yrs.)	0-20	21-30	31-40	41-50	51-60	61-70	>70
Males	1	6	6	7	5	5	2
Females.....	0	13	9	15	17	8	0
Total.....	1	19	15	22	22	13	2

SYMPTOMATOLOGY

The symptoms presented below are given in their order of frequency (Fig. 1). The most frequent complaints were the triad of diarrhea (94.6 per cent), weakness (88.3 per cent) and weight loss (84.1 per cent). Over one-third of the patients with diarrhea (36.3 per cent) had more than six bowel movements a day. Diarrhea was intermittent with a greater incidence of watery stools (43.8 per cent) during the period of acute symptoms than of the classical, pale, bulky stools (30.3 per cent). The character of the diarrhea was not adequately described in 20.5 per cent. Normal appearing bowel movements were present at all times in 4.2 per cent of patients while 1.2 per cent were constipated. These patients may fall in the group termed latent or occult steatorrhea (17, 18) or incomplete sprue (11).

Loss of weight ranged from seven to 60 pounds with a mean weight loss of 25.3 pounds. This degree of weight loss was comparable to those given by others (2, 4, 5, 7, 11). The majority of the patients (70.1 per cent) lost more than 15 pounds at some time in the course of their illness. Weight loss of as much as 50 per cent of the normal body weight has been observed by us and by others (5, 7, 13, 14).

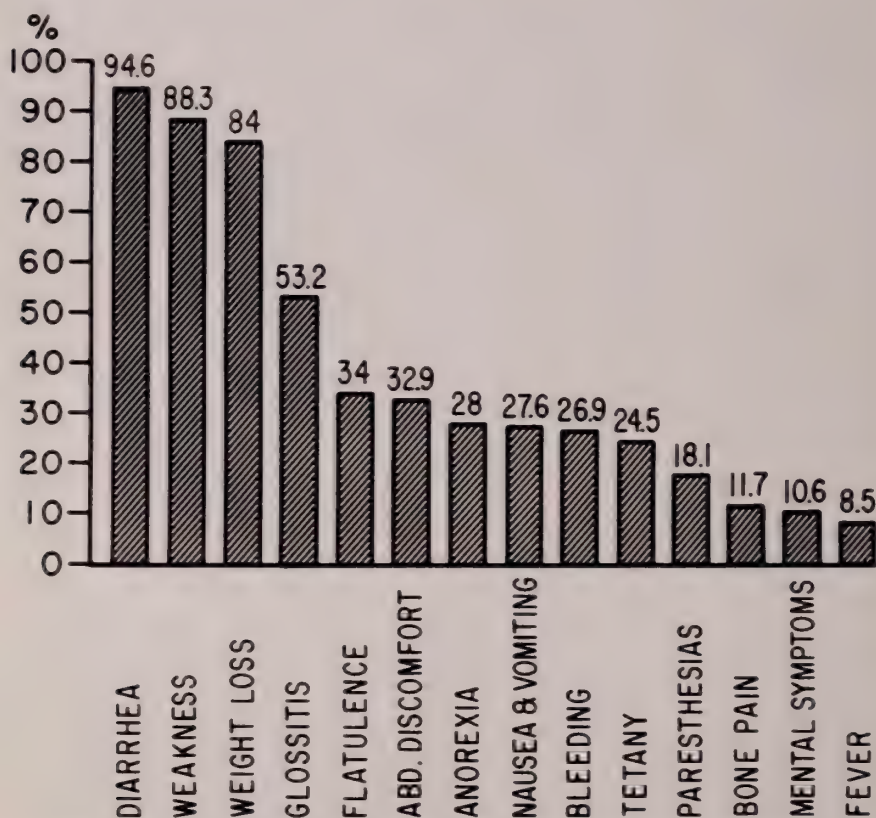


FIG. 1. Major symptoms observed in 94 patients with idiopathic sprue.

Glossitis and stomatitis of some degree was noted in 53.2 per cent of patients. The incidence was lower than that reported in previous reviews (7, 9, 11). The explanation may lie in the generally improved diet in more recent years resulting in lower occurrence of vitamin deficiencies. Recent reports from Havana and Puerto Rico have indicated a lower incidence of tropical sprue in these countries in recent years. This change has also been attributed to the improved nutrition of the population (19). That glossitis in sprue is not exclusively a result of avitaminosis B has been noted by others (15), so this may not be the sole explanation for the reduced incidence of this symptom.

Vague abdominal discomfort (pain, burning, cramps), flatulence, nausea and vomiting were noted by almost all of the patients. Severe abdominal pain, however, was uncommon and when present usually indicated major complications such as intestinal obstruction (volvulus), bleeding or an intercurrent disease, i.e., cholecystitis, appendicitis. Anorexia was found in about 25 per cent of patients. Voracious appetite, noted by Thaysen (2, 20) and Cooke (4) in their series, was not a prominent feature and was noted only in milder cases or after the patients showed clinical improvement.

Hemorrhagic manifestations were noted in 26.6 per cent of patients, a higher incidence than previously noted. They varied in severity from skin petechiae to fulminating gastrointestinal hemorrhage. These cases are reported in greater detail elsewhere in this symposium (21).

Tetany was observed in 24.5 per cent of patients; this incidence compares well with the occurrence reported by other observers (5, 7). Bone pain was complained of by 11.7 per cent. Tetany occurred usually in patients who were suffering a severe exacerbation. The comparatively low incidence of clinical tetany, as compared to the presence of low serum calcium levels, may be related to the associated hypoproteinemia which results in relatively higher levels of ionized calcium in the serum. Paresthesias were present in 18.1 per cent.

Severe mental changes occurred in 11 patients. In five instances there was frank psychosis (one patient was on steroid therapy (22)), and the remaining six patients exhibited varying degrees of depression, anxiety or character disorders.

Subnormal body temperature was more common than low grade fever; definite fever was usually associated with intercurrent infections. Patients with sprue have a diminished resistance to infection even during remission. It has also been observed that infections, seemingly innocuous, often precipitate a relapse of the disease (7). There were some instances of unexplained temperature elevations.

SIGNS

The observed signs are summarized in order of frequency in Figure 2. Emaciation was the most common sign (64.9 per cent). The initial body weight ranged from 67 to 167 pounds; the mean weight was 104 pounds (males 116 pounds, females 98 pounds). A large number of patients showed abdominal distention (37.2 per cent) and dependent edema (36.2 per cent). The former was due mostly to distended loops of small bowel which not infrequently were visible on the abdominal wall. Distention due to ballooning of the colon was also observed frequently. Ascites, as part of anasarca, was rare (two patients).

Hepatomegaly occurred in 30.8 per cent of the group. The enlargement of the liver was usually not more than one to two finger's breadth below the costal margin. Splenomegaly of mild degree was present in 6.3 per cent. The higher incidence of hepato-splenomegaly, as compared with the observations of others (12), was probably caused by the large number of Puerto Rican patients in whom parasitic infestation was common.

The mean systolic blood pressure (64 patients) was 105 millimeters of mercury. In 28.9 per cent of this group the systolic blood pressure was below 100 millimeters of mercury. Hypotension was a feature which persisted during remission as has been seen by others (2, 20). Clubbing of fingers and/or toes was found in 22.3 per cent, a figure unchanged from the previous study.

Less common manifestations were pigmentation (11.7 per cent) and dryness (9.6 per cent) of the skin. In some instances the pigmentation was extensive and included the lips and buccal mucosa. Dry skin was often a manifestation of vitamin A deficiency. No instances of pellagra were encountered. The decreased

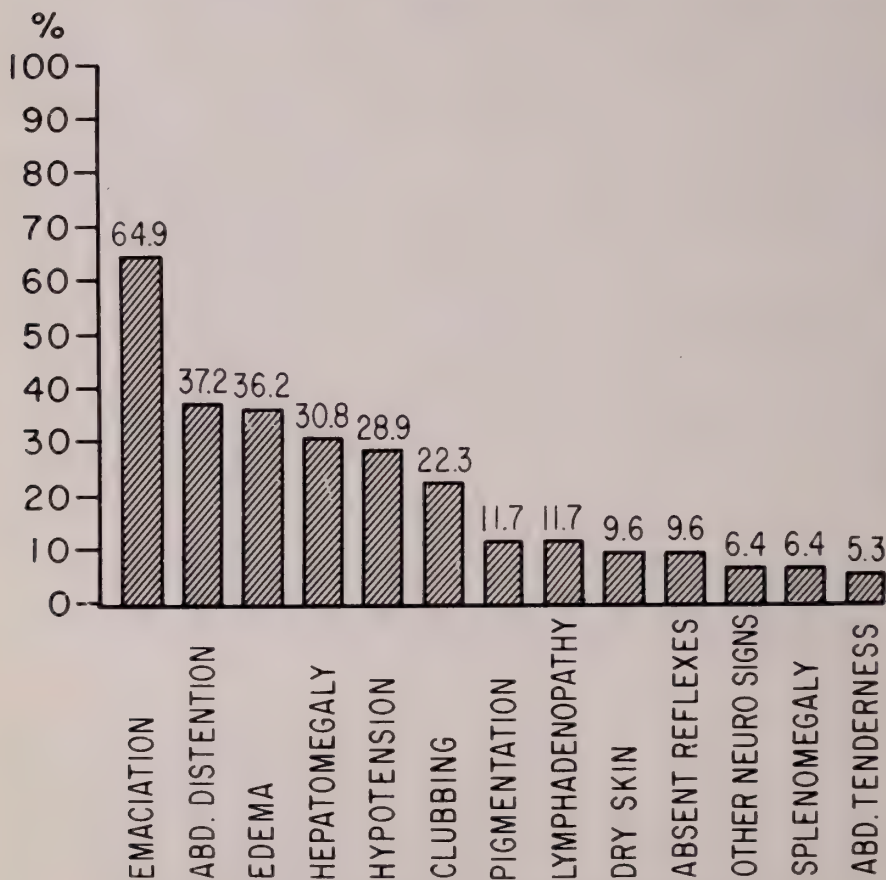


FIG. 2. Major signs observed in 94 patients with idiopathic sprue.

incidence of these signs compared with the earlier study may be related again to the improved nutritional state of the population.

Abnormal neurologic signs were present in 16.0 per cent of patients. Absent deep tendon reflexes was the commonest finding. Lesions of the central nervous system with severe disability were also encountered and were similar to those described by other observers (5, 9, 11, 12). Three patients presented varying manifestations of posterior and lateral column involvement. In none was there histamine-achlorhydria. One patient (with a history of lues) had a clinical picture of cervical tabes. One patient had a transient Brown-Séquard syndrome. These neurologic findings are presented in detail elsewhere in this symposium (23).

Moderate lymphadenopathy was noted in 11.7 per cent of patients. Abdominal tenderness occurred only in 5.3 per cent and was thus rare in uncomplicated sprue.

HEMATOLOGIC PICTURE

The hematologic findings in these patients are presented in Table II and III. The peripheral blood picture of sprue is characterized by anemia which is often macrocytic and associated with a megaloblastic bone marrow. In many instances, however, iron deficiency anemia may be a prominent feature with an erythroid marrow (24). Impairment of iron absorption has been demonstrated in studies

TABLE II
Laboratory data in sprue patients

Determination	No. of Patients	Mean	Range
Hemoglobin (gm./l.)	81	9.3	2-14.9
Red blood count (M/cu.mm.)	73	3.1	0.66-4.8
White blood count (/cu.mm.)	75	5,918	1700-12,800
ESR (mm./hr.)	25	29.3	3-104
Gastric acidity (units)	45	42.3	0- >100
Total protein (gm.%)	62	5.7	3.4-7.7
Albumin (gm./l.)	55	3.3	1.7-4.7
Sodium (mEq./l.)	18	138.4	128-145
Potassium (mEq./l.)	18	4.2	1.8-5.5
Calcium (mg./l.)	69	8.1	4.4-11.4
Phosphorus (mg.%)	57	3.0	1.2-4.6
Alkaline phosphatase (K-A units)	38	16.5	5.4-44.0
Fasting blood sugar (mg.%)	65	79.3	45-115
Total cholesterol (mg.%)	76	162	80-340
Esterified cholesterol (mg.%)	31	112	61-173
Phospholipids (mg.%)	42	203	93-315
Total lipid (mg.%)	42	584	175-1110
Vitamin A (μ g.%)	55	31.3	0-124
Carotene (μ g.%)	55	56.3	0-420
Vitamin B ₁₂ excretion (%)	23	2.9	—
Fecal fat, total (%)	54	38.0	11.2-71.6
Fecal fatty acid (%)	26	25.4	8.2-44.3

TABLE III
Incidence of abnormal laboratory data in sprue patients

Anemia (Hb. < 5 gm.%)	14.1%
(Hb. < 10 gm.%)	51.5%
(RBC < 3.5 million/cu.mm.)	55.4%
Megaloblastic bone marrow	33.3%
Erythroid bone marrow	20.0%
Leukopenia (WBC < 5,000/cu.mm.)	37.3%
Anisocytosis	37.3%
Hypoprothrombinemia	70.2%
Elevated sedimentation rate (>30 mm./hr.)	28.1%
Thrombocytopenia (<100,000/cu.mm.)	13.2%
Achlorhydria	13.1%
Hypoproteinemia (<5 gm.%)	19.4%
Hypoalbuminemia (<3.5 gm.%)	51.7%
Hypoglycemia (<70 mg.%)	12.2%
Hypocalcemia (<9.0 mg.%)	66.2%
Hypokalemia (<3.5 mEq./l.)	16.7%
Hypophosphatemia (<2.5 mg.%)	28.3%
Increased alk. p'tase (>10 K-A units)	61.5%
Hypocholesteremia (<150 mg.%)	50.0%
Hypophospholipidemia (<200 mg.%)	59.5%
Hypolipemia (total lipids < 500 mg.%)	40.5%
Abnormal liver chemistries	21.4%
Flat glucose tolerance test	92.0%
Flat vitamin A tolerance test	81.1%
Diminished vitamin B ₁₂ absorption	87.0%
Steatorrhea (>15%)	93.1%
(>25%)	75.9%
Abnormal pancreatic function	14.3%
Small bowel "sprue pattern"	87.3%
Osteoporosis (osteomalacia)	59.5%

with radioactive isotopes (25). In 51.1 per cent of patients the hemoglobin level was less than 10 gm. per cent and in 14.1 per cent was below 5. The mean level was lower than those noted in other series (4, 7). In the majority of patients (63.0 per cent) the red blood count was below 3.5 million per cu. mm. Macrocytes were present in 37.3 per cent of 67 patients. Leukopenia (white blood count below 5,000 per cu. mm.) was noted in 37.3 per cent. Thrombocytopenia (platelets below 100,000 per cu. mm.) was noted in 13.2 per cent (53 determinations). The high incidence of leukopenia and thrombocytopenia may reflect the interaction of multiple deficiencies such as vitamin B₁₂ folic acid and iron. No instances of aplastic anemia were encountered as has been observed in tropical sprue (26).

The bone marrow was studied in 30 patients and was normal in 36.7 per cent, megaloblastic in 33.3 per cent, erythroid in 20.0 per cent and showed other non-diagnostic alterations in 10.0 per cent. In the 10 patients with megaloblastic bone marrow, only one had associated achlorhydria. Because of the limited number of bone marrow aspirations these figures cannot be assumed to be generally representative of the bone marrow in sprue.

The prothrombin time was determined in 37 patients and was prolonged more than three seconds over the control sample in 70.2 per cent. This high incidence of hypoprothrombinemia may be correlated with the large number of hemorrhagic phenomena observed in the present group of patients. Again, this determination was done most often in cases where a history of bleeding was obtained so that a true incidence of hypoprothrombinemia in sprue was not obtained.

Gastric analysis yielded a 13.1 per cent incidence of histamine-achlorhydria. The mean free acid concentration was 42.3 units. These figures come close to those noted in the earlier survey from this hospital (7). This figure coincides with the incidence of achlorhydria in a normal population of comparable age (14) and suggests that achlorhydria is not an essential feature of the sprue syndrome, in contrast to pernicious anemia.

BLOOD CHEMICAL STUDIES

The chemical blood analyses reflected the malnourished state of the patients. Hypoproteinemia, hypoalbuminemia, hypoglycemia and hypolipidemia occurred in a large number. The levels observed coincided with figures given in the previous review and by others (5, 7, 11, 20, 27).

Serum total proteins were low (Table II and III) and in 57.7 per cent the serum albumin was below 3.5 gm. per 100 ml., a considerably higher proportion of hypoalbuminemia than was seen in England (4). This may be a reflection of a more severe disorder observed in the present group of sprue patients.

There was a high incidence of hypocalcemia (66.2 per cent) which correlated with an elevation of serum alkaline phosphatase (61.5 per cent) and bone demineralization. The mean serum phosphorus level was low and concentrations below 2.5 mg. per 100 ml. were observed in 28.3 per cent. These findings indicate malabsorption of minerals and vitamin D compatible with osteomalacia.

Hypokalemia was noted in 16.7 per cent of patients. Hypokalemia in sprue patients (potassium levels of 2.5 to 3.0 mEq. per l.) with attendant clinical symptoms of profound muscle weakness, mental apathy and personality changes has been recently stressed (4). In our series, while serum potassium levels below 3.5 mEq. per l. were seen, they occurred mostly in patients in severe relapse. However, a tendency to comparatively low potassium levels has been observed in patients in remission.

Hypoglycemia (fasting blood sugar level below 70 mg. per 100 ml.) was noted in 12.2 per cent of patients. Serum lipid levels were generally depressed, with the most marked decrease in serum total and esterified cholesterol. Mean levels of serum total and esterified cholesterol were 162 and 112 mg. per 100 ml., respectively. Serum phospholipids averaged 203 and total lipid 584 mg. per 100 ml. Low levels of serum lipids have been reported by others (11, 20, 27). Cholesterol levels below 150 mg. per 100 ml. were observed in 50.6 per cent of patients while low levels of phospholipids (below 200 mg. per 100 ml.) and total lipid (below 500 mg. per 100 ml.) were observed in 59.5 per cent and 40.5 per cent respectively. Serum levels of vitamin A and carotene were also low, with mean figures of 31.3 and 56.3 μ g. per 100 ml., respectively. Despite low carotene levels, three

instances of carotenemia were encountered (325, 346 and 420 $\mu\text{g.}$ per 100 ml.). These three patients had normal vitamin A absorption.

The abnormalities observed in liver function were of a mild degree. Slight increase in serum bilirubin in the absence of clinical jaundice, or some impairment of bromsulphalein excretion were noted in 21.4 per cent of 42 patients examined. These findings may be correlated with the known effect of malnutrition on liver function.

ABSORPTION TESTS AND SPECIAL STUDIES

Absorption tests were carried out in the majority of patients. An oral glucose tolerance test was performed on 75 patients. In 92 per cent the curve was flat (Table III) with a mean elevation from a fasting level of 79 to a peak level of 111 mg. per 100 ml. after ingestion of 100 grams of glucose. The occurrence of a flat glucose tolerance test in sprue has been confirmed by many investigators since Thaysen's original observation (2). In six cases the oral glucose tolerance test was normal. In one patient, a known diabetic, the curve was extremely high and was not included in determining the average figures.

An oral vitamin A tolerance test was performed in 55 instances. The mean fasting level was 31.3 $\mu\text{g.}$ per 100 ml. and rose to a mean peak level of 53.3 after ingestion of 180,000 units of vitamin A given as oleum percomorphum. The finding of normal absorption of vitamin A in oil in some patients with sprue could not be correlated with normal glucose absorption, nor was there any strict relation to the degree or presence of steatorrhea or of the sprue pattern of the small bowel on x-ray examination. Absorption of radioactive vitamin B₁₂ given orally was studied in 23 patients (Schilling test). The mean urinary excretion was 2.9 per cent of the administered dose, compared to a normal mean excretion level of 18 per cent. Depressed excretion was found in 87 per cent of patients (Table III). There was no increase in absorption in sprue patients when intrinsic factor was added. These observations are reported in detail elsewhere (28).

Pancreatic function studies were carried out in 21 patients. A decrease in enzyme secretion was demonstrated in 14.3 per cent (Table III). This again may be related to effects of malnutrition.

Quantitative analysis of fecal fat was done in 58 patients. Steatorrhea (fecal fat above 15 per cent of dry weight) was present in 93.1 per cent. Fecal fat levels above 25 per cent were noted in 75.9 per cent of patients (Table III). The mean total fat level was 38.0 per cent of dry weight of feces. In four patients the fecal fat excretion was reported below 15 per cent of dry weight. The explanation for the low fat excretion may lie in the restricted dietary fat intake at the time of examination. The importance of this factor has been emphasized previously (7).

ROENTGEN STUDIES

Roentgen examination of the small intestine was performed in 71 patients. A sprue pattern (29-31) (dilatation, late segmentation, thickened folds, hypersecretion) was demonstrated in 87.3 per cent (Table III). X-ray changes were seen in the duodenum in 12.7 per cent of these patients; small intestinal transit time

was increased in 6.3 per cent and decreased in 14.3 per cent. Studies of the colon by barium enema were obtained in about half of the patients in whom the small bowel had been examined. No abnormalities were present except for marked dilatation in cases with advanced sprue. Sigmoidoscopy, performed in 24 patients, was negative in all instances except that pallor of the mucosa was seen in a few cases.

The bones were examined roentgenologically in 37 patients. In 40.5 per cent there was no abnormality. Slight demineralization was present in 10.8 per cent; moderate or severe osteoporosis (osteomalacia) was noted in 35.2 and 13.5 per cent, respectively. Fractures were observed in 16.2 per cent and were unrelated to trauma. Ribs were involved in three patients, the femur on two occasions, and vertebrae, scapula and clavicle each in one instance. One patient was severely dwarfed. A detailed discussion of the bone abnormalities in sprue is presented elsewhere (32).

COMPLICATIONS

Complications noted in this series included intestinal obstruction in four patients. In two instances volvulus of the sigmoid occurred (both patients died). One patient had volvulus of the cecum demonstrated on exploration. In one patient peritoneal adhesions were found at operation. The occurrence of such complications has been commented on elsewhere (33). No additional cases have been added in the present series. One patient, whose course was complicated by recurrent abdominal pain and gastrointestinal hemorrhages, died and had multiple ulcerations of the small intestine (34).

Septicemia with gram-negative organisms occurred in two patients. Although low-grade fever was encountered in a small per cent of cases previously reported (7), no instances of sepsis were found. Both patients were severely ill, with other major complications including bleeding and tetany. The finding of a gram-negative organism (*E. coli* and *A. aerogenes*) suggested an origin from the bowel.

ASSOCIATED CONDITIONS

Carcinoma of the gastrointestinal tract was discovered in five patients with prolonged courses of idiopathic sprue. Three patients developed gastric carcinomas 9, 13 and 17 years after sprue was diagnosed; one had carcinoma of the esophagus 12 years later and one had a carcinoma of the ascending colon three years afterwards. In the last three instances the lesions were surgically resected. In all but two patients the symptoms of sprue were in remission when symptoms of the carcinoma became manifest. While the development of gastrointestinal malignancies in patients with long-standing, idiopathic sprue is of interest, any relationship between the two conditions is obscure. In view of the small number of these cases observed, a comparison with the established high incidence of gastric carcinoma in pernicious anemia is not warranted at the present time. It should be emphasized, however, that co-existing gastrointestinal neoplasm should be considered if suspicious symptoms develop, rather than attribute the latter entirely to the sprue syndrome.

No patients had evidence of bacterial pathogens or parasites in the stool while under observation. Three patients had a history of intestinal parasitism and two of dysentery.

Two patients had diabetes mellitus prior to hospitalization for sprue; one patient subsequently developed diabetes. The association of these two disorders is infrequent in our observation. It is necessary to rule out pancreatic dysfunction as a common etiology and to eliminate the possibility of diabetic visceral neuropathy as a cause of diarrhea and steatorrhea (8). Thompson has noted an increased incidence of diabetes in patients with celiac disease (35).

Three patients had a proven duodenal ulcer prior to hospitalization for the sprue syndrome. Eight patients had a history of syphilis and/or positive serology. Two patients had hypertension, in one this developed subsequent to steroid therapy, while the other had known hypertension for 20 years. A past history of tuberculosis was given by two patients; one had pulmonary involvement and the other cervical adenitis.

EFFECT OF MANAGEMENT ON SYMPTOMS AND SIGNS

The patients were treated with a variety of agents (24, 36-39). Two patients received only the conventional sprue diet (low-fat, high-protein, high-calorie, bland, low-residue) with multiple vitamin supplements. In 45 patients parenteral liver extract was added to the regimen. Four patients received oral folic acid in addition to liver extract. In nine patients parenteral vitamin B₁₂ was administered, in addition to liver extract and folic acid. Thirty-four patients, who failed to respond adequately to diet and anti-anemic therapy were then placed on steroid therapy in addition. After an initial response was obtained the patients were maintained for long periods on minimal dosages of steroids. Initially, corticotrophin and cortisone were used, followed in turn by hydrocortisone and more recently by prednisone and prednisolone.

The response to therapy was classified according to the following categories: (a) remission; (b) full clinical control; (c) partial clinical control; (d) no change; (e) fatal termination (Table IV).

Six patients achieved complete remission, i.e., became asymptomatic without

TABLE IV
Comparison of results of conventional and steroid therapy in sprue

Management	Remission	Full Clinical Control	Partial Clinical Control	No Change	Deceased	Total
Conventional						
No.	6	20	20	4	10	60
%	10.0	33.3	33.3	6.7	16.7	
Steroid Therapy						
No.	0	20	12	1	4	34
%	0	58.8	26.5	2.9	11.8	
Total						
No.	6	40	29	5	14	94
%	6.4	42.5	30.9	5.3	14.9	

therapy. Five of these had been treated with crude liver extract and one patient with a combination of liver extract and vitamin B₁₂. Five of these patients were Puerto Rican. The non-Puerto Rican patient was asymptomatic without treatment for 10 years before her death in an old age home.

Forty patients were fully controlled with prolonged therapy. Seventeen of these patients were controlled with liver extract; one with liver extract and folic acid; two with liver extract, folic acid and vitamin B₁₂; and 20 with all three anti-anemic factors plus steroid therapy.

Improvement and partial clinical control with therapy resulted in 29 patients. One received diet and vitamins alone; 13 were given liver extract; one received liver extract with folic acid; five had liver extract, folic acid and vitamin B₁₂; and 9 were given all these agents plus steroids.

No change was observed in five patients. One received diet alone, two had liver extract, one was given liver extract and folic acid, and one received steroids.

Of the 14 patients whose death was attributable to sprue, eight were receiving liver extract; one, liver extract and folic acid; one, liver extract, folic acid and vitamin B₁₂; and four, steroid therapy in addition to the other three factors. Of the four patients who received steroids and died, one was the patient previously described with abdominal pain, gastrointestinal bleeding and ulcerations (34); the others were treated inadequately or only terminally. A more detailed discussion of the current management of sprue is presented elsewhere in this symposium (41).

Response to therapy resulted in a diminished number of bowel movements with semi-formed or formed stools. Appetite improved rapidly, followed by marked gain in weight. A feeling of well being supplanted the initial lassitude and weakness. Glossitis subsided. Macrocytic anemia responded well to specific therapy. Abdominal distention and flatulence often persisted despite cessation of diarrhea. Even under full clinical control, in many instances there was a tendency to loose bowel movements under conditions of emotional stress, intercurrent infection and dietary indiscretion. Consistent hypotension was observed in many sprue patients whose symptoms were well controlled. Rapid correction of signs of avitaminosis usually occurred and such features as cheilosis, dry skin and hemorrhagic phenomena due to hypoprothrombinemia subsided.

More resistant to correction were the objective evidences of malabsorption such as the various tests of carbohydrate and fat absorption, steatorrhea, and the sprue pattern of the small intestine. While improvement was noted, complete return to normal did not occur in the more severe forms of the disorder.

In some patients isolated selective defects persisted during periods of good clinical control, such as tetany and hypocalcemia, bone pain, fractures and osteomalacia, iron deficiency anemia, subacute combined degeneration and other neurologic abnormalities, hypoproteinemia and edema.

SYMPTOMS AND SIGNS IN PUERTO RICANS VERSUS NON-PUERTO RICANS

The group of 23 patients of Puerto Rican nativity was deemed worthy of separate scrutiny. Those patients in whom the onset of symptoms occurred while in Puerto Rico could be considered to have tropical sprue. Since a disorder

like sprue presents multiple symptoms, and relapses and remissions over a long period of time, it is difficult to assign the exact time at which the disease became manifest. The majority of patients reported symptoms before emigrating to the United States and could be considered as having the tropical variety of sprue. Therefore, all patients from Puerto Rico were considered separately for comparison. They provided a contrast to the 71 non-Puerto Rican patients who had developed sprue in temperate climates.

A number of differences were apparent (Table V). The mean duration of symptoms prior to hospitalization was considerably shorter in Puerto Ricans (2.3 years versus 8.8 years). There was a higher incidence of glossitis (74.1 per cent) and paresthesias (26.1 per cent) among Puerto Rican patients, while tetany (8.7 per cent) and bleeding (8.7 per cent) were less frequently observed. Differences in signs in the tropical group included a higher incidence of hepatomegaly (52.2 per cent) and splenomegaly (17.4 per cent) and a lower incidence of clubbing (8.7 per cent). Among these patients, severe anemia was encountered more frequently; 34.8 per cent had hemoglobin levels below 5 gm. per cent. In 89 per cent of examinations, the bone marrow was megaloblastic. Macrocytosis and leukopenia (74.0 per cent) were also more common in Puerto Ricans. Serum albumin levels were higher (4.0 gm. per 100 ml.). The mean serum calcium was slightly higher (8.8 mg. per 100 ml.) and a level below 7 was observed only once in 17 determinations on Puerto Rican patients as compared with an incidence of 32.4 per cent in non-Puerto Ricans. This may be correlated with the less frequent occurrence of bone demineralization among these patients (20 per cent). The only fatality in this group occurred after appendectomy, while the sprue syndrome was in remission. Response to therapy was better among Puerto

TABLE V
Comparison of clinical and laboratory data in Puerto Rican and non-Puerto Rican patients with sprue

	Non-Puerto Rican	Puerto Rican
No. of patients.....	71	23
Duration of symptoms.....	8.8 yrs.	2.3 yrs.
Glossitis.....	46.5%	74.0%
Bleeding.....	33.8%	8.7%
Tetany.....	29.6%	8.7%
Clubbing.....	26.8%	8.7%
Hepatomegaly.....	25.4%	52.2%
Paresthesias.....	15.5%	26.1%
Splenomegaly.....	2.8%	17.4%
Megaloblastic bone marrow.....	9.5%	89.0%
Hemoglobin < 5 gm.%.....	7.0%	34.8%
Leukopenia.....	24.6%	74.0%
Bone demineralization.....	65.6%	20.0%
Calcium < 7 mg.%.....	38.9%	5.9%
Mortality.....	26.7%	4.5%
Cured.....	1.7%	21.7%

Rican patients. In five patients remission was effected. In 12 patients full clinical control was induced by conventional therapy. Six patients were partially controlled, only one of whom required steroid therapy. No therapeutic failures were encountered.

These differences in symptomatology, signs and therapeutic response among Puerto Rican patients with sprue have been observed by others (5, 9, 42). An explanation may lie in the earlier recognition and treatment of these patients who present mainly with hematologic disturbances rather than more profound metabolic derangements. That sprue in Puerto Rico need not necessarily be associated with macrocytic anemia and deficiency states (glossitis) has recently been emphasized by Gardner (19) who recognized an early malabsorption syndrome without these features in military personnel in Puerto Rico.

DISCUSSION

Sprue as a Problem in Diagnosis. The diagnosis of idiopathic sprue in the typical case presents no difficulties. The physician is confronted by a middle-aged person who has had a long history of intermittent diarrhea, periods of marked and rapid weight loss, severe weakness and usually a sore mouth and tongue. There is a variety of abdominal complaints including flatulence, discomfort or nausea. Often either hemorrhagic phenomena, tetany or paresthesias are present. The patient is poorly nourished and moderately pale. Often the abdomen is distended and dependent edema may be present. The blood pressure is low. Clubbing of fingers or toes may be present. A few significant laboratory tests confirm the diagnosis. Anemia is usually present, often associated with a megaloblastic bone marrow in the absence of achlorhydria. The prothrombin time is prolonged. Serum albumin is usually below 3.5 gm. per 100 ml. and serum calcium is less than 9.0 mg. per 100 ml. along with an increase in alkaline phosphatase. All serum lipid fractions are low. The glucose and vitamin A tolerance curves are flat. There is evidence of diminished absorption of vitamin B₁₂. Steatorrhea is present along with a sprue pattern on roentgenologic examination of the small intestine. The bones are demineralized on roentgenologic examination.

Aside from such patients, there is a group of milder or incomplete clinical instances that remain diagnostic problems. Some otherwise typical patients have no diarrhea, although steatorrhea is present. In other instances, a major presenting symptom such as severe bleeding (due to hypoprothrombinemia) (43), fractures (due to osteomalacia) (17, 18), or intractable edema (due to hypoproteinemia) (44) may mask the underlying disorder which may be of a mild character. Patients are often seen who have been partially responsive to therapy and thereby resemble a *forme fruste* of the disease (7).

Comparison of old and new series. In comparing the present review with the study presented from this hospital in 1947 (7), some differences are apparent. While 36 patients with primary sprue were reported in the 15 year period from 1931 to 1946, 64 patients with long follow-up periods were seen in the 10 year

period from 1946 to 1956. The increased number is probably due to greater awareness of the disease rather than an actual increase in the incidence of sprue.

The clinical features of the disease were strikingly similar in both the old and new series, including the long duration of disease prior to recognition and the major complaints. There was a lower incidence of glossitis in the present series, with an increased incidence of hemorrhagic phenomena. The physical findings compared favorably, with the exception of a decreased incidence of skin pigmentation and an increased number of neurologic abnormalities. Laboratory data were remarkably alike. The mortality was higher in the earlier review than in the present series, even though the number of patients in remission in recent years was less. This may reflect the fact that milder forms of sprue may now be suppressed by the increased availability of a better diet or earlier treatment with liver extract and vitamin B₁₂. On the other hand, more severe forms of the disorder which do not respond to such conventional therapy improve with steroids.

Complications and associated diseases in the present survey include intestinal obstruction, severe gastrointestinal hemorrhage and ulcerations, septicemia, gastrointestinal malignancies, diabetes mellitus and duodenal ulcer. Although the first complication has been recognized in the past (33), the others are newly described associated features, the significance of which is not fully apparent at present.

Tropical versus non-tropical sprue. The opportunity to make observations on tropical sprue was afforded by the inclusion of a number of patients born in Puerto Rico. While the separation is somewhat artificial, since the symptoms might have developed either in Puerto Rico or in New York, differences from the non-Puerto Rican sprue patients were observed. The typical Puerto Rican patient presented with symptoms of shorter duration. Glossitis was prominent. Paresthesias were often noted; but tetany, hemorrhagic phenomena and clubbing were rare. Hepatomegaly was usual, and splenomegaly was not infrequent. There was a high incidence of severe macrocytic anemia, leukopenia and a megaloblastic bone marrow. Very low serum calcium levels were rare and bone demineralization uncommon. Osteomalacia was seen only in 1 patient and is rarely observed in tropical sprue (5, 9). One may speculate that increased exposure to sunshine and thereby increased availability of vitamin D may be responsible.

Tropical sprue has been similarly characterized by other observers and the same differences from non-tropical sprue were apparent (5, 9, 26, 27, 42). While there is ample evidence that sprue is a single disorder, genetically transmitted and probably an inborn error of metabolism (1, 2, 4, 8, 27, 45), clinical varieties do exist. The trigger mechanism of sprue in the tropics remains to be elucidated. The impaired nutritional state with multiple dietary inadequacies and higher incidence of parasitic infestation may be important factors.

Tropical sprue has been considered a disorder curable by a single course of therapy (27). However, evidence is accumulating that asymptomatic patients may present objective signs of the metabolic disorder, such as malabsorption of carbohydrates and fats, steatorrhea and roentgenologic abnormalities of the

small intestine (19). Similar observations have been made in children who have recovered from celiac disease (46) and in non-tropical sprue (31), suggesting that celiac disease, tropical and non-tropical sprue represent varying manifestations of the same basic disorder.

SUMMARY

Ninety-four patients with idiopathic sprue, including 23 patients born in Puerto Rico (tropical sprue) were studied.

The disorder was characterized by long duration of symptoms, chiefly, diarrhea, weakness, weight loss, glossitis and abdominal flatulence. Hypotension, tetany, clubbing and hemorrhagic manifestations were prominent signs. Laboratory features included megaloblastic anemia, hypoproteinemia, hypocalcemia and hypolipidemia. Malabsorption was evidenced by steatorrhea, flat glucose and vitamin A tolerance curves, and impaired absorption of radioactive B_{12} . The typical roentgenologic appearance of the small intestine was encountered.

Unusual complications included volvulus of the cecum or sigmoid and septicemia. A small number of patients developed carcinoma of the gastrointestinal tract; the significance of this observation is obscure.

The effect of various types of therapy on the course of the disease was studied. Differences in symptoms and signs and in the response to therapy were found in the Puerto Rican patients (tropical sprue).

Emphasis was placed on the diagnostic problem presented by patients with atypical or incomplete forms of the disorder.

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THE BLOOD AND BONE MARROW IN IDIOPATHIC SPRUE

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Anemia is a characteristic accompaniment of the malabsorption syndromes. So regular is the occurrence of anemia in the primary sprues that, in the words of Cooke and co-workers, "we have come to regard persistently normal blood values as a strong evidence against the diagnosis" (1). Sooner or later, most or all untreated patients with sprue show anemia (2), although at any given time—for example, at the time of initial medical examination—the incidence of anemia varies according to differences in the severity of the disease (3). It is the purpose of this report to review the hematologic disturbances in primary sprue, and to discuss their significance and pathogenesis in the light of current concepts and modern technics of study.

DEFINITIONS

Celiac disease, tropical sprue and non-tropical sprue are now generally considered different manifestations of the same basic pathophysiologic disturbance (1). The terms "sprue" and "malabsorption syndrome" may properly be applied to all three. Thaysen's term "idiopathic steatorrhea" includes all three disorders (4), but some British workers (5) restrict the identical phrase—idiopathic steatorrhea—to only celiac disease and non-tropical sprue, considering that tropical sprue is a different disorder. We shall use the terms "sprue," "malabsorption syndrome," and "idiopathic steatorrhea" interchangeably to include all three forms of the disturbance, but shall specify (for hematologic reasons which will become apparent shortly) "celiac disease" when that entity is under discussion.

MATERIALS

Included in this report are studies on 94 patients with idiopathic sprue. The diagnosis was established following clinical and laboratory studies which included gastrointestinal x-rays, stool examinations for fat, glucose and vitamin A tolerance tests, pancreatic studies and hematologic studies. The details of these patients are presented in another paper in the present symposium (6). Initial hematologic studies were tabulated and analyzed, and the results are summarized in Table I. Studies of intestinal absorption of vitamin B₁₂ were made in 25 of the patients and are discussed elsewhere (7). The results of these hematologic studies are also listed in Tables II, IV, V, and VI.

THE ANEMIA

In 1928, Carmichael-Low found macrocytosis "as a general rule" in all of 150 cases of tropical sprue, and macrocytic anemia in 60 per cent (8). In 1929, Serra

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TABLE I
Hematology of Author's Cases of Idiopathic Sprue

	Number of Cases	Mean	Range
Hemoglobin gm./100 ml.	94	9.3	2.4-15.5
Red Cells millions cu. mm.	83	3.11	0.66-5.7
Hematocrit %	29	33.5	12-46
White Cells per cu. mm.	83	5,900	1,700-13,800
Polymorphonuclear Leukocytes per cu. mm.	83	1,600	1,050-12,600
Lymphocytes per cu. mm.	83	2,000	600-5,900
Platelets per cu. mm.	54	195,000	30,000-520,000
Sedimentation Rate (Westergren) mm. in 1 hour	32	29	3-104
Prothrombin Time (one-stage) seconds	37	19.5 (control, 12.7)	10.5-51

reported macrocytic anemia in 89 per cent of 45 cases of tropical sprue (9). In 1930, Manson-Bahr and Willoughby, in describing 200 cases of tropical sprue, again reported macrocytosis for the entire series, and macrocytic anemia in 46 per cent (10).

This pattern of observation has continued (11-22), so that studies of over 2,400 cases of tropical sprue, non-tropical sprue, and idiopathic steatorrhea throughout the world have established the general rule that the characteristic erythropoietic disturbance in the malabsorption syndrome is the development of macrocytosis, due to megaloblastic erythropoiesis in the bone marrow. When the patient is sufficiently sick, macrocytosis is superseded by macrocytic, megaloblastic anemia (Table II).

In the mildest cases, and when treatment is adequate, there is no anemia, but macrocytosis may still be present (19). In less early cases, macrocytosis without anemia may still be seen (16, 17, 19); or, alternatively, normocytic (23) or normocytic hypochromic (3, 21) anemia may occasionally be noted. As the disorder progresses, the anemia becomes more severe and frankly macrocytic, with a megaloblastic marrow (3, 14). Superficially, this severe macrocytic anemia resembles pernicious anemia (see below).

Macrocytosis is reported in 50 to 100 per cent of cases of sprue sufficiently symptomatic to visit the physician. According to Cooke and co-workers (1), two-thirds of patients with sprue show macrocytosis when first seen, and all such patients show macrocytosis sooner or later under continued observation. Macrocytic anemia is reported in from 14 to 95 per cent of untreated cases of sprue (3, 16, 17, 22).

In occasional cases, the anemia of sprue is hypochromic (14, 17, 21, 24, 25, 26). The incidence varies from 6 to 17 per cent of unselected uncomplicated cases. In celiac disease, as opposed to the other forms of the malabsorption syndrome, the anemia, when it is present, is regularly hypochromic (21).

In rare cases, aplastic anemia has been reported (3). The "hemolytic anemia" described in the older literature (8) has not been substantiated.

Among the author's 94 cases of idiopathic sprue, macrocytosis was found in 57.6 per cent, while 33 per cent were normocytic, and 9.4 per cent hypochromic at the time of initial observation (Table I). The type of anemia sometimes changed during prolonged observation. Thus, in 6 of the author's cases, macrocytosis was present on some occasions, and normocytosis in others. In 3 cases, hypochromia was present on some occasions, and normochromia and normocytosis on others. One patient's anemia was macrocytic, normocytic, and hypochromic at different times in her course.

In these 94 patients, the mean hemoglobin was 9.3 grams, and anemia of 10 grams or less occurred in 51 per cent of the cases. The mean red cell count was 3,110,000; 55 per cent of the patients had less than 3,500,000 red cells when first observed. These findings agree substantially with those in the literature.

TABLE II
Reports of the Blood Picture in Sprue

Reference	No. Cases	Diagnosis	Location	Blood Picture
Carmichael-Low (8)	150	Tropical Sprue	England	Macrocytosis in practically all
Serra (9)	45	Tropical Sprue	Puerto Rico	Macrocytic anemia in 60%
Fairley (11)	63	Tropical Sprue	India	Macrocytic anemia in 89%
Baumgartner (12)	36	"Sprue"	N. Y. State	Macrocytosis in over 50%
Manson-Bahr (10)	200	Tropical Sprue	England	Macrocytic anemia in 45%
Suarez (13)	70	Tropical Sprue	Porto Rico	Macrocytosis in all
Castle (14)	92	Tropical Sprue	Porto Rico	Macrocytic anemia in 46%
				Macrocytic anemia in 91%
				Macrocytic anemia in 94%
				Hypochromic anemia in 6% (selected cases)
Thaysen (4)	45	Non-tropical Sprue	Denmark	"Hyperchromic" anemia in 66%
Suarez (15)	150	Tropical Sprue	Porto Rico	Macrocytosis in 99%
Rodriguez-Molina (16)	100	Tropical Sprue	Porto Rico	Macrocytosis in 90%
Keele (17)	80	Tropical Sprue	British in India	Hypochromia in 17%
				Macrocytosis in 56%
				Macrocytic anemia in 26%
				Hypochromic anemia in 9%
Adlersberg (18)	36	Idiopathic Sprue	N. Y. City	Macrocytic anemia in 53%
Stefanini (3)	1069	Tropical Sprue	Italians in India	Macrocytic anemia in 14%
Innes (19)	17	Tropical Sprue	Scotland	Aplastic anemia in 0.3%
	27	Non-tropical Sprue		Macrocytosis in 80%
				Macrocytosis in 67%
				Hypochromia in 15%
Cooke (20)	33	Idiopathic Steatorrhea	England	Color index high in 66%
Lopez (52)	155	Tropical Sprue	Cuba	Macrocytic anemia in 100%
				(selected cases)
Present report	94	Idiopathic Sprue	N. Y. City	Macrocytic anemia in 58%
				Hypochromic anemia in 9%

SPRUE VS. PERNICIOUS ANEMIA

In the older literature, the fact that macrocytosis and megaloblastic erythropoiesis occurred both in pernicious anemia and in the malabsorption states led a number of workers to report that the peripheral blood in the two conditions is identical (16). However, it was early established that the two disorders were not the same (9, 14). It is only in certain very severe cases that the anisocytosis, poikilocytosis, leukopenia, thrombocytopenia and normoblastosis which occur in pernicious anemia are found in sprue (3). The hematologic resemblance between the two disorders results from the same basic process: malabsorption of erythropoietic substances from the diet. However, the reasons for the malabsorption are different, and the blood picture in sprue may be distinguished from that in pernicious anemia by a number of features (Table III):

TABLE III
Pernicious Anemia vs Sprue Anemia

	Pernicious Anemia	Sprue
Type of Anemia	Macrocytic	Usually macrocytic—rarely, hypochromic
Pancytopenia	Common	Rare
Blood smear	Anisocytosis and poikilocytosis regularly present	Anisocytosis and poikilocytosis uncommonly found
Bone marrow	Megaloblastic	Sometimes megaloblastic
Gastric Juice	Achlorhydria always	Often "intermediate"
Neurologic Symptoms	Common	Achlorhydria uncommon
Serum B ₁₂	Very low	Rare
Intestinal absorption of vitamin B ₁₂	Always impaired	Low in some; normal in some
	Improved by intrinsic factor	Usually impaired
		No effect from intrinsic factor

TABLE IV
Incidence of Hypochromic Anemia in Non-Celiac Sprue

Reference	No. Cases	Diagnosis	Location	Incidence of Hypochromic Anemia
Castle (14)	92	Tropical Sprue	Porto Rico	6%
Rodriguez-Molina (16)	100	Tropical Sprue	Porto Rico	17%
Keele (17)	80	Tropical Sprue	British in India	9%
Innes (19)	44	Tropical and Non-tropical Sprue	Scotland	0%
Stefanini (3)	1069	Tropical Sprue	Italians in India	0%
Hawkins (26)	200	Steatorrhea	England	6.5%
Present report	94	Idiopathic Sprue	N. Y. City	9%

1. In pernicious anemia, the blood smear shows not only macrocytosis, but marked variation in size and shape of the red cells. In the macrocytic anemia of sprue, poikilocytosis and anisocytosis are not prominent, and may be absent (9, 20).

2. In pernicious anemia, the bone marrow is frankly megaloblastic. In sprue with macrocytic anemia, the bone marrow may also be megaloblastic (3, 14), but in many cases it is rather "intermediate" or "transitional" in character (1, 18, 19, 27).

3. In pernicious anemia, achylia is the rule. In sprue, most cases show free gastric hydrochloric acid, and many with initial achlorhydria have a return of free acid under therapy.

4. In pernicious anemia, neurologic symptoms occur in 80 per cent of cases, and posterolateral sclerosis occurs in up to 70 per cent (28). In sprue, neurologic findings are present in less than 2 per cent, and posterolateral sclerosis is a rarity (29).

5. In pernicious anemia in relapse, the serum level of vitamin B₁₂ is always low. In sprue with macrocytic anemia, two types of cases may be distinguished: those with low serum B₁₂, and those in which the serum B₁₂ is normal (30, 31).

6. In pernicious anemia, the absorption of orally administered vitamin B₁₂ is always impaired, both in relapse and in remission; and absorption is improved by a potent source of intrinsic factor. In sprue, the intestinal absorption of vitamin B₁₂ is usually, but not invariably, impaired; intrinsic factor does not enhance absorption.

Sprue is therefore to be considered in the differential diagnosis of any patient who presents with what seems to be Addisonian pernicious anemia, and the two disorders can be distinguished with the aid of the new methods of study of vitamin B₁₂. When such studies are made in groups of patients who for years have borne the diagnosis "pernicious anemia," a few patients will often be found in whom the diagnosis is rather sprue.

HYPOCHROMIC ANEMIA IN SPRUE

In contrast to all other varieties of idiopathic sprue, whose typical hematologic abnormality is a megaloblastic, macrocytic anemia, celiac disease characteristically shows a hypochromic, microcytic anemia (19, 21, 34, 35). This is an iron-deficiency anemia, and is often refractory to treatment with oral iron preparations—i.e., there is impaired absorption of iron in the gastrointestinal tract.

A similar iron-deficiency anemia is occasionally seen in the non-celiac varieties of idiopathic sprue, instead of the usual macrocytic anemia (14, 16, 17, 19, 24, 25). In the present series, iron-deficiency was found in 9 per cent of the cases. Sometimes, there is a combination of macrocytosis and hypochromia; sometimes, there is only hypochromia; rarely, both hypochromia and microcytosis are present. This iron-deficiency anemia is notoriously refractory to treatment with oral iron (5, 24, 26) and may require parenteral iron therapy for relief (26). The sternal marrow in such cases shows normoblastic hyperplasia with or without some "intermediate" erythropoiesis (26); it is never frankly megaloblastic.

TABLE V
The Bone Marrow In Non-Celiac Sprue

Reference	No. Cases	Megaloblastic	"Inter- mediate"	Normal	Other
Krjukoff* (36)	16	16	—	—	—
Rhoads* (37)	22	22	—	—	—
Adlersberg (18)	12	4	5	2	1 "fatty"
Innes (19)	18	6	7	5	—
Stefanini** (3)	25	22	—	3	5 "aplastic"
Lopez (17)	155	155	—	—	—
Cooke (1)	49	17	21	11	—
Friedlander (38)	12	7	—	—	5 not stated
Gardner (39)	19	19	—	—	—
Present Report	27	10	6	10	1 "fatty"

* Surgical sections; others were marrow aspirations.

** More than one marrow study in some cases.

THE BONE MARROW IN SPRUE

When macrocytic anemia is present in a patient with sprue, the bone marrow is "megaloblastic" (Table V). As the patient goes into remission, erythropoiesis becomes normoblastic, and the marrow tends to return to normal. It is notable that the "megaloblastic" bone marrow in sprue is often not identical with that in pernicious anemia, but that the erythropoiesis is best described as "intermediate"—i.e., the red cell precursors show features of both megaloblastic and normoblastic maturation. Such "intermediate" or "transitional" erythropoiesis has subtle morphologic features which distinguish it from both normoblastic and frankly megaloblastic erythropoiesis (27). The presence of such features in a patient with supposed or atypical pernicious anemia should lead to a search for some other diagnosis, such as malabsorption syndrome.

The marrow findings in sprue are summarized in Table V. In the author's series, 27 marrow aspirations were done, of which 10 were megaloblastic, 6 "intermediate", 10 normal, and 1 fatty. Giant myelocytes and metamyelocytes were occasionally noted. In patients with sprue who are incompletely remitted, the blood shows macrocytosis without anemia, and the marrow shows "intermediate" erythropoiesis (19). Marrow aplasia has rarely been reported in sprue (3). Aplasia has not been noted in the present series.

THE OTHER BLOOD FINDINGS IN SPRUE

The white blood cell count in sprue is not remarkable, although leukopenia due to granulocytopenia has been reported in from 2 to 68 per cent of cases (Table VI). Leukocytosis occurs in less than 10 per cent of cases. In the present series, the mean white cell count was 5,900, and 31 per cent of the patients showed a white count of less than 5,000 per cu.mm. The mean granulocyte count was 4,600 per cu.mm.; 27.5 per cent of the patients showed a granulocyte count of less than 3,000 per cu.mm. The mean lymphocyte count was 2,000—i.e., lymphocytosis was only relative, not absolute. A lymphocyte count of over 4,000 per

TABLE VI
The Leukocyte Count in Sprue

Reference	No. Cases	Normal White Count	Leukopenia	Leukocytosis
Carmichael-Low (8)	114	85%	8%	7%
Manson-Bahr (10)	198	93%	2.5%	4.5%
Rodriguez-Molina (16)	99	44%	56%	0%
Stefanini (3)	153	32%	68%	0%
Innes (19)	43	79%	14%	7%
Present Report	83	63%	31%	6%

cu.mm. was present in only 4 of 83 cases (4.8 per cent). Overall leukocytosis occurred in only 5 cases (6.1 per cent), including two who showed absolute lymphocytosis. These findings are in general agreement with those in the literature. In the majority of cases of sprue (61 per cent in this series), the white blood count is normal, and the differential count unremarkable.

Qualitative changes in the leukocytes, similar to those seen in pernicious anemia, may be present in sprue. Rodriguez-Molina (16) noted giant band cells in a few cases and macrocytosis of the leukocytes in general. Hyperlobulation of the neutrophils was noted in occasional cases (9, 16). These changes are much less frequent than in pernicious anemia. They were present in only one of the author's patients.

The platelets are usually normal (3, 16, 18). Of 54 cases examined in this series 8 (15 per cent) showed platelet counts below 100,000 per cu.mm. (direct method). There were no associated clinical findings of thrombocytopenia.

Nucleated red cells are only occasionally seen in the peripheral blood (9, 16), typically when the anemia is severe (red cells under 2 million per cu.mm.). They were noted in 7 cases of the author's series (7.5 per cent): 6 showed normoblasts, and one showed megaloblasts.

The hypotonic fragility of the red cells was found to be decreased by some workers (20), but most noted it to be normal (3, 9).

The sedimentation rate was tested by the Westergren method in 32 patients. The mean was 29.3 mm. in one hour; 18 results (56 per cent) were less than 20 mm.; and 23 (72 per cent) were less than 30 mm. in one hour. Nine patients (28 per cent) showed sedimentation rates over 30 mm.

Prothrombin time was estimated by the one-stage method in 37 patients, of whom 26 (70 per cent) showed a prothrombin time which was more than 3 seconds greater than that of the control. The mean prothrombin time was 19.5 seconds; the mean normal 12.7 seconds. Hypoprothrombinemia is discussed in a separate paper in this symposium (40), and the entire problem of hemorrhage in sprue is reviewed by Cooke (1) and others (41).

GASTRIC ACIDITY

Free hydrochloric acid is the rule in the malabsorption syndromes, although hypochlorhydria is often present. Histamine-fast achlorhydria occurs in from 1

to 15 per cent of patients with primary sprue (3, 9, 20, 39, 42). In the present series, 8 of 61 patients examined lacked free acid, even after histamine (13 per cent). In many cases of sprue with achlorhydria, free acid returns after successful therapy (42).

GASTRIC CYTOLOGY

Patients with untreated tropical sprue showed changes in squamous epithelial and the columnar cells of the stomach which were similar to those described in pernicious anemia (39). Treatment, however, was slowly followed by return of the gastric epithelium towards normal—a change which does not occur in pernicious anemia.

PATHOGENETIC STUDIES OF THE ANEMIAS OF SPRUE

The resemblance between the usual macrocytic anemia of sprue and the macrocytic anemia of pernicious anemia is the result of the megaloblastic erythropoiesis which is common to both disorders. Megaloblastic erythropoiesis results when certain essential factors are lacking at the marrow, notably vitamin B₁₂ and folic acid. In pernicious anemia, it has been established that the deficiency is that of vitamin B₁₂, which cannot properly be absorbed by the patient with pernicious anemia because he lacks "intrinsic factor." In the sprue syndrome, intrinsic factor is irrelevant but malabsorption of vitamin B₁₂, folic acid and perhaps other materials is responsible for disturbed erythropoiesis at the marrow.

In 1935, Thaysen suggested that the "hyperchromic" anemia in sprue might be due to deficient absorption of an extrinsic factor present in the diet (4). Castle and Rhoads (14) suggested that, at least in most cases of sprue, the nature of the absorptive difficulty differed from that in pernicious anemia. More recently, the response of some cases of sprue to folic acid but not to vitamin B₁₂ (43, 44, 45, 50), and of others to vitamin B₁₂ but not to folic acid (31), has suggested that the absorptive defect might be different in different cases of sprue itself. Furthermore, it has been recognized that changes in the intestinal mucosa might be caused by dietary deficiency itself (46), which might in turn lead to malabsorption of dietary materials—a self-perpetuating cycle.

Cases of sprue show many absorptive defects (vitamin B₁₂, folic acid, fat, vitamin A, glucose, etc.). It seems likely that these difficulties in absorption are manifestations of metabolic abnormalities of various enzymes in the intestinal mucosa. The occurrence of sprue in families, and the past history of celiac disease in patients with sprue, suggest that the basic disturbance in sprue is somehow genetically transmitted. Of the multiple absorptive difficulties in sprue, those of especial hematologic interest have to do with vitamin B₁₂, folic acid, proteins and iron.

Vitamin B₁₂. Cases of sprue may be divided into those whose serum levels of vitamin B₁₂, during relapse, are low; and those in which it is normal (31, 50). Correspondingly, malabsorption of vitamin B₁₂ from the intestinal tract is found

in some, but not all, cases of idiopathic sprue (33, 47, 48, 49). The low serum B_{12} , when present, is a reflection of depleted tissue (marrow) stores of vitamin B_{12} . There is no apparent difficulty of utilization of B_{12} ; when sprue patients with low serum B_{12} levels receive B_{12} parenterally, they regularly show hematologic response (31). This is in contrast to patients with untreated sprue whose serum B_{12} is normal; they do not respond to B_{12} therapy, but require folic acid for remission (31).

Twenty-five of the present series of cases were studied with regard to their ability to absorb vitamin B_{12} from the intestinal tract (7). Twenty patients (80 per cent) showed impaired absorption of B_{12} ; in five patients (20 per cent), the absorption was normal. This impairment of B_{12} absorption is not dependent upon or improved by intrinsic factor (7, 32, 33, 48, 49)—i.e., the defect differs from that seen in pernicious anemia. However, as in pernicious anemia, it was found, in the present series of cases, that the inability to absorb orally administered vitamin B_{12} does not disappear when the patient with sprue is in remission (7).

Folic acid. Malabsorption of folic acid from the intestinal tract was found in all 8 patients with the sprue syndrome studied by Girdwood (51). No such abnormality was found in 15 cases of pernicious anemia, in 4 cases of anemia of pregnancy with megaloblastic or transitional marrow, or in 14 control individuals.

Proteins and other factors. Hypoproteinemia is a frequent finding in the sprue syndrome (52). This may be a reflection of poor absorption of dietary protein from the intestinal tract, or perhaps impaired synthesis of protein from its precursors in the body. Since proteins are necessary for normal erythropoiesis, deficient absorption and synthesis of proteins may well be factors in the impaired production of blood elements in sprue.

Owren (53) has described a "liver protein synthesis factor" which was necessary to relieve macrocytosis and hypoprothrombinemia in patients with idiopathic steatorrhea and pernicious anemia, whereas B_{12} and folic acid failed to cause remission of these features. Malabsorption of this postulated factor is assumed. Others have described other such factors, present only in crude liver extracts (54, 55).

The defect in fat absorption in sprue leads to malabsorption of vitamin K precursors, with resultant hypoprothrombinemia. In some cases, the hypoprothrombinemia seems to be due to other mechanisms, such as folic acid deficiency itself (56).

Iron. In a small proportion of patients with the malabsorption syndrome, the anemia which develops is iron-deficient. Studies have suggested, however, that perhaps all patients with idiopathic steatorrhea have a defect in the absorption of iron from the intestinal tract (24). It is not known whether this is part of a general failure of absorption, or is due to a deficiency in apoferritin in the intestinal mucosa. In addition, however, it seems probable that there is excessive loss of iron in some cases.

Pathogenesis of the Anemias of Idiopathic Sprue

Normal hematopoiesis depends, among other things, on the presence of normal amounts of vitamin B₁₂, folic acid, protein precursors and iron at the bone marrow. Deficiency of folic acid or of vitamin B₁₂ at the sites of blood cell formation results in abnormal "megaloblastic" erythropoiesis, with resultant macrocytic anemia. In idiopathic sprue, defective absorption of many substances is present, including vitamin B₁₂ and folic acid. In some cases, it is primarily malabsorption of dietary vitamin B₁₂ which leads to the hematologic picture; in others, apparently, malabsorption of folic acid is the more important feature.

In most cases of sprue, however, it is presumably defective intestinal absorption of multiple dietary constituents—proteins, vitamin B₁₂, folic acid, other substances—which gives rise to the resultant picture in the blood: macrocytic, megaloblastic anemia.

It is of great interest that the inability of the intestinal tract to absorb vitamin B₁₂ and folic acid persists whether the patient is in remission or in relapse (7, 51). This is in contrast to the situation in certain patients with secondary sprue, notably patients with intestinal blind loops and stasis, in whom impaired vitamin B₁₂ absorption disappears when successful treatment with antibiotics is undertaken (57, and unpublished personal observations). In idiopathic sprue, then, as in pernicious anemia, the patient with idiopathic sprue always has the potential of developing megaloblastosis and macrocytic anemia, unless treatment is undertaken to ensure adequate supplies of malabsorbed materials to the bone marrow and other tissues.

Since there is also deficient absorption of iron from the gastrointestinal tract in some, if not all, patients with idiopathic sprue, there is a potentiality of developing iron-deficiency anemia. In actual fact, only a small percentage of sprue patients develop an anemia which is iron-deficient, and factors other than malabsorption (notably, loss of iron) may be responsible for the fulfillment of the potential of iron-deficiency. Utilization of iron is normal in such patients, and the use of parenteral iron, circumventing the intestinal defect, allows remission. The inability to absorb iron normally has been suggested to be the factor which is responsible for the occurrence of "intermediate" rather than frankly megaloblastic erythropoiesis in the macrocytic anemia of sprue (27).

SUMMARY

The changes in the blood and the bone marrow in idiopathic sprue have been discussed. Celiac disease is accompanied by an iron-deficiency anemia. Adult forms of the malabsorption syndrome—idiopathic sprue, idiopathic steatorrhea, tropical sprue—are accompanied by macrocytosis in almost all cases, and by various degrees of macrocytic anemia in cases of varying severity.

There are multiple intestinal defects of absorption in idiopathic sprue. Those of importance in the development of the hematologic picture include malabsorption of dietary protein, folic acid, vitamin B₁₂ and iron. Replacement of the

deficient materials at the centers of blood formation is necessary for remission of the hematologic abnormalities.

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HEMORRHAGIC MANIFESTATIONS IN IDIOPATHIC SPRUE: A REPORT OF 25 CASES AND REVIEW OF THE LITERATURE

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Severe bleeding is reportedly a rare manifestation of sprue (1, 2). When present it is a result in almost all instances of severe hypoprothrombinemia due to vitamin K deficiency (3-11). The most common sites of bleeding are the skin and subcutaneous tissues, although epistaxis, melena, hematuria, hemoptysis, menorrhagia and hemarthrosis have been reported. To our knowledge, no such complications have been observed in tropical sprue except where aplastic anemia with thrombocytopenia supervenes (12-14).

The present study reports 25 patients in whom hemorrhagic phenomena were a prominent feature of idiopathic sprue. Seven of these patients are presented in detail. These patients were encountered in a review of 82 sprue patients selected for this study from a larger number of patients observed at The Mount Sinai Hospital, New York City, from 1931 to 1956. A detailed analysis of the clinical observations of this group is presented elsewhere in the symposium (27).

CLINICAL MATERIAL

The total group included 27 men and 55 women ranging in age from 16 to 73 years at the time of first hospital admission with a mean age of 48 for the males and 45 for the females. The majority of patients had diarrhea with steatorrhea, abdominal distention and marked weight loss. All had evidence of malabsorption of carbohydrate and/or fat. In most instances an abnormal small bowel x-ray pattern was demonstrated, with dilatation, late segmentation and increased secretion. Symptoms had been present for from one month to 52 years before initial hospitalization; the average duration of symptoms was 6.2 years. Ten patients were observed only for the duration of hospitalization. Seventy-two patients were followed for a period of from six months to 22 years, with an average follow-up period of 5.1 years. Thirty of these patients are still under continuous observation at the present time. Thirteen patients died from the disease.

Twenty-two patients, eight men and 14 women, were from Puerto Rico. Because of the difficulty in setting the time of onset of the disease, the number of patients in this group who developed symptoms while in Puerto Rico could not be ascertained with certainty. Thus, the actual number who might be considered as true instances of tropical sprue could not be determined. Megaloblastic anemia was the presenting feature of these patients.

The group with hemorrhagic manifestations included seven men (mean age 48) and 18 women (mean age 43), two of whom were Puerto Rican. Symptoms

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TABLE I
Clinical data of sprue patients with hemorrhagic manifestations

Case No.	Sex Age	Yr. of Admission	Bleeding Manifestations	Prothrombin Time (seconds) Patient/Control	Duration of Disease	Other Complications	Follow-up
1	F 52	1930	G. I. Bleeding	—	1 yr.	Tetany	Died 1933, no autopsy.
2	F 21	1932	Hemorrhage, post-tonsillectomy	—	5 mos.	Tetany, edema	Died 1944 in tetany. Autopsy — thrombosis dural sinus, cervical veins; fatty liver.
3	F 52	1933	Severe epistaxis	—	3 wks.	Megaloblastic anemia	—
4	F 60	1934	Melena, 4 yrs. before	—	20 yrs.	Bone pain, Glossitis	Remission, 1948.
5*	F 50	1940	Occ. epistaxis	—	2 mos.	Osteoporosis, anemia	21 yrs., steroid therapy 6 yrs.
		1935	Ecchymoses, epistaxis	—			
		1945	Hematuria, mod. ecchymoses	35/15			
		1950	Mod. ecchymoses	18/13		Tetany	
		"	Massive ecchymoses	100		Edema	
		1951	Hematuria	120			
		1952	Mod. ecchymoses	60/12			
6*	F 41	1935	Epistaxis, petechiae, ecchymoses, hematemesis, bleeding gums	—	3 yrs.	Tetany	Died, autopsy—multiple visceral hemorrhages.
7	M 64	1936	Epistaxis	—	—	—	Remission after 10 yrs., carcinoma of esophagus 16 yrs. later.
8	F 29	1937	Menorrhagia, 7 yrs.	—	3 mos.	Glossitis, megaloblastic anemia.	Remission, 1940
9	F 30	1940	Ecchymoses	—	10 yrs.	—	16 yrs., steroid therapy 6 yrs.
		1952	Ecchymoses	35/14		Volvulus of cecum (16)	
10*	F 60	1941	Epistaxis, bleeding gums, ecchymoses	55/24	1 yr.	Anemia, osteoporosis	Remission, 1943. Died, 1951 in an old age home.

TABLE I—Continued

Clinical data of sprue patients with hemorrhagic manifestations

Case No.	Sex	Yr. of Admission	Bleeding Manifestations	Prothrombin Time (seconds) Patient/Control	Duration of Disease	Other Complications	Follow-up
11*	M	1941	Ecchymoses, melena, petechiae	70/23	2 yrs.	Osteoporosis, anemia, hiatus hernia	—
		1944	Melena, epistaxis	120/30			
		1944	Hematuria and subconjunctival hemorrhage	(25%)			
12	M	1943	Hematemesis, melena	3%	3 mos.	—	Died 1944, autopsy—acute yellow atrophy of liver.
13	F	1945	G.I. bleeding, epistaxis, bleeding gums	47/15	1 yr.	Tetany	—
14	F	1945	Petechiae, purpura	32/18	2½ yrs.	—	—
15	F	1946	Purpura	31/24	3 yrs.	—	—
16*	M	1948	Ecchymoses	128/12	17 yrs.	Osteoporosis, fracture of femoral neck	8 yrs., steroid therapy 6 yrs.
17*	F	1949	Ecchymoses	21/12	11 mos.	Osteoporosis, edema.	Died 1951, no autopsy.
		1950		30/13		Hemoglobinuria, E. Coli septicemia	
		1951	Melena	>3 min.		Tetany	
18	M	1951	Melena	14/12.5	1 yr.	—	Died 1953, autopsy—multiple ulcerations small intestine (15)
		1952	Melena				
19	F	1953	Purpura	16.5/12.5	9 mos.	—	3 yrs. steroid therapy.
20	F	1953	Ecchymoses, epistaxis	—	2 yrs.	—	—
21	M	1953	Bleeding gums, purpura (1952)	—	2 yrs.	C.V.A. 1952	Steroid therapy, 2 yrs.
22	F	1954	Purpura (history)	—	5 yrs.	Tetany	2 yrs.
23*	M	1954	Ecchymoses, epistaxis	80 sec.	Several mos.	Old duodenal ulcer Edema, A. aerogenes septicemia	2 yrs., steroid therapy, 1 yr.
24	F	1954	Ecchymoses (history)	—	11 yrs.	Tetany	2 yrs., steroid therapy, 2 yrs.
25	F	1954	Gum bleeding	27/11	23 yrs.	Tetany, diabetes 30 yrs., edema	Steroid therapy, 2 yrs.,

* Indicates cases presented in detail.

had been noted in this group of patients for from one month to 23 years before admission, with an average duration of 3.6 years. Six of the deaths attributable to sprue occurred in this group of patients.

The clinical characteristics of the 25 patients with bleeding manifestations are presented in Table I. Severe bleeding into the skin (petechiae, ecchymoses, purpura) was the most frequently observed hemorrhagic manifestation, occurring on 19 occasions in 15 patients. Epistaxis was the next most common kind of bleeding and was observed in ten patients. Melena was noted by eight patients, bleeding gums by five, hematuria and hematemesis by two and post-operative hemorrhage and menorrhagia, each in one patient.

In 14 patients determination of the prothrombin time (one-stage) was performed at the time of bleeding. The values were abnormal in 13 instances, ranging from 21 seconds to more than three minutes (control 12 seconds). None of these patients had any evidence of liver disease. In all instances, after the administration of vitamin K the prothrombin time returned to normal. In patient 13, whose case is presented in detail elsewhere, melena was observed on two occasions and the prothrombin time was not prolonged. This patient subsequently died elsewhere and at autopsy multiple ulcerations of the small intestine were demonstrated (15).

Other complications noted in this group of patients were: tetany in nine instances and osteoporosis in six; edema was present in five patients; severe anemia was present in four; severe glossitis in two; septicemia in two; and volvulus of the cecum, an associated duodenal ulcer, unexplained hemoglobinuria and diabetes mellitus were each noted in one patient.

CASE REPORTS

Condensed case histories are presented for seven of these patients, three men and four women, in whom hemorrhagic phenomena were severe and fulminating.

Case 23

S. B., a 36-year old man, was hospitalized in April 1954 because of leg pains for five days and epistaxis for one day. He had noted intermittent fever for nine months; weakness, anorexia and a 14-pound weight loss in the preceding two weeks; and one to two watery bowel movements daily for several months. A duodenal ulcer diagnosed in 1940 recurred in 1945 and 1946. X-ray examinations performed in 1951 and 1952 revealed an old duodenal ulcer, retention of barium in the duodenum, coarsening of the mucosal pattern of the small bowel with dilatation and segmentation. On physical examination at admission in April 1954 he was emaciated and acutely and chronically ill. The temperature was 104°F., pulse 100 per minute and blood pressure 130/70. The lips and nostrils were excoriated and crusted with blood. The calves and extensor surfaces of both thighs were tender and warm. Large ecchymoses were noted over the left upper pretibial area. Laboratory studies are presented in Table II. The suspected diagnosis of leukemia was ruled out by negative peripheral blood and bone marrow examinations. The studies performed to determine the coagulation defect indicated severe hypoprothrombinemia. The platelet count was normal, 200,000 per cmm. with a normal bleeding time of five minutes. The fibrinogen content was also normal, 250 mg. per cent. The clotting time was prolonged to 25 minutes. The prothrombin time was markedly prolonged to 80 seconds. The prolonged prothrombin time of more than two minutes, obtained with a 10 per cent dilution, ruled out a labile factor deficiency. The

TABLE II
Laboratory Data of 7 Patients during Acute Episodes of Hemorrhagic Manifestations Due to Hypoprolthraemia

Pt.	Date	HGB, gm. %	WBC, cu. mm.	Plts., cu. mm.	Alb., gm. %	Glob., gm. %	Ca, mg. %	Cholest., mg. %	Alk. P _{base} , K.A.	Glucose Tol. Test mg. % 0 Max.	Vit. A Tol. Test gamma % 0 Max.	Carotene gamma %	Fecal Fat % Dry Wt. Neutral fat Fatty acids
23. (S. B.)	Apr. '54	9.3	6,800	220,000	2.3	3.5	8.8	127	48	102	25	46	11 32 12
17. (R. B.)	May '49	9.1	8,000	120,000	3.8	2.8	9.6		24	60	29	82	38 41†
	Dec. '51	2.7	13,000	120,000	2.2	1.9	5.4	142	12				
16. (P. S.)	July '48	9.9	5,250	190,000	3.9	1.4	9.1	200	28	80	32	37	9 20 28
11. (M. S.)	Mar. '41	50.0*	2,400				8.3						18†
10. (N. M.)	Mar. '41	46.0*	7,100	260,000	3.7	2.0	8.7	220	36	47	15	6	15.5†
6. (L. H.)	July '35	14.0*	1,950	180,000			7.6			75			
5. (S. H.)	Aug. '45	8.6	5,600	185,000	2.8	1.6	8.6		15	80	53	78	16 50†
	July '50	8.8	6,000	140,000	3.0	2.7	6.9	143	31		15	87	38 17 40
	Sept. '50	4.5	6,700	120,000	2.0	1.6	7.3	143	18	91	20	29	5 23 39
	Apr. '52	10.2	6,500	190,000	3.6	2.6	8.7	160	8		56	83	

* Expressed in per cent † Indicates total fecal fat, % dry wt.

absence of a circulating anticoagulant was proven by plasma-mixing experiments showing that addition of the patient's plasma to normal plasma did not prolong the clotting time of the latter. The blood culture was positive for *Aerobacter aerogenes*. Gastrointestinal x-ray examination confirmed the previous findings.

After vitamin K therapy the muscle pain and bleeding subsided. The clotting time returned to a normal of 11 minutes while the prothrombin time fell to a normal of 12.8 seconds. The presence of malabsorption, steatorrhea and small bowel deficiency pattern on x-ray suggested the diagnosis of non-tropical sprue as the etiology of the hypoprothrombinemia. The fever was attributed to septicemia and responded to Chloromycetin. The anemia was corrected by transfusion. The patient gained 12 pounds and was discharged.

The patient was readmitted in August 1954 for diarrhea, nausea and a weight loss of 17 pounds. The fingers were clubbed and the abdomen distended with visible loops of bowel. The prothrombin time was normal, 13.5 seconds (control 12 seconds). Therapy consisted of a high caloric-low fat diet, crude liver extract, parenteral vitamin B₁₂, oral iron, vitamins (including folic acid), deodorized tincture of opium, Banthine and calcium.

He was again hospitalized in October 1954 for bronchopneumonia associated with a relapse of the sprue syndrome. In August 1955, after development of pedal edema and a weight loss of 30 pounds, prednisone was started and the patient improved. He was maintained on 12.5 mg. of prednisone daily in addition to previous therapy. His weight rose to 150 pounds and all symptoms of sprue were controlled.

Comment. A 36-year old man, presenting with fever, skin and muscle hemorrhages, and epistaxis, was initially suspected of leukemia. Bleeding was due to severe hypoprothrombinemia, corrected by administration of vitamin K. There was associated septicemia. While in the Hospital, steatorrhea was present without diarrhea. Malabsorption and small bowel "deficiency pattern" were demonstrated, leading to a diagnosis of idiopathic sprue. Recurrent episodes of diarrhea and malnutrition supervened but were controlled by steroid therapy.

Case 17

R. B., a 63-year old woman, was hospitalized in May 1949 because of an ecchymosis covering the left upper extremity of four days duration, and weakness for three months. Nine months before she had been hospitalized because of leg pains, anorexia, fatigue and a 10-pound weight loss. Bone x-rays showed severe osteoporosis. The iliac marrow showed cells suggestive of myeloma. The patient was treated with stilbamidine and urethane. Physical examination at the present admission revealed a large ecchymosis of the left arm and forearm with swelling and warmth over the lower biceps. Clubbing of the fingers was present. Laboratory data revealed moderate anemia and malabsorption with steatorrhea (Table II). The bone marrow showed increased erythropoiesis and numerous megakaryocytes. Prothrombin time was 21 seconds (control 12 seconds). A barium meal revealed an abnormal small bowel pattern with dilatation, segmentation and thickened folds. The bleeding was ascribed to hypoprothrombinemia resulting from malabsorption. After administration of vitamin K the prothrombin time was normal, 12 seconds. The patient was treated with diet, vitamins, including B₁₂ and D, and calcium. At no time during this admission was there any diarrhea.

The patient was subsequently hospitalized three times for severe episodes of diarrhea between August 1949 and June 1950, and once in March 1950 for unexplained hemoglobinuria. The serum calcium fell to 7.4 mg. per cent and the prothrombin time was prolonged, 30 seconds (control 13 seconds). She became cachectic with ankle edema, dry skin, thin hair and marked atrophy of the tongue margins. The patient was apparently refractory to the conventional therapy but refused adrenocorticotrophic hormone. She had an episode of shaking chills and fever with a positive blood culture for *E. coli*. Transfusions were given

frequently. On occasion, melena was noted. She was hospitalized for the last time in December 1951 because of increased weakness, bone pain, edema and melena. There was pallor, abdominal distention and tenderness, and carpopedal spasm. She had severe anemia, hypocalcemia and hypoalbuminemia (Table II). The prothrombin time was more than three minutes (Table I). She became semicomatose and disoriented, despite supportive measures. Following administration of intravenous ACTH she improved temporarily but three weeks later developed severe tetany, lapsed into coma and died. Post-mortem examination was refused.

Comment: A 63-year old woman was hospitalized because of massive ecchymoses and bone pain attributed to severe osteoporosis. Bleeding was ascribed to hypoprothrombinemia corrected by administration of vitamin K. Steatorrhea was found without diarrhea. X-ray of the small bowel showed a deficiency pattern. Subsequently, the patient had severe diarrhea, anemia, edema, tetany and again hypoprothrombinemia with melena. She had one episode of unexplained hemoglobinuria and a transient septicemia. She deteriorated progressively and died two and one-half years after the initial bleeding episode.

Case 16

P. S., a 50-year old man, was hospitalized in July 1948 because of multiple painful ecchymoses of the buttocks and extremities following venipuncture and intramuscular injections. In 1931 the patient first noticed diarrhea with two to four watery, foul, fatty, tan-colored bowel movements daily. There was flatulence and abdominal distention. In 1944, he was put on a bland diet with bananas supplemented with vitamins, liver extract and folic acid. Diarrhea persisted and he lost 44 pounds. On physical examination, the patient was pot-bellied and poorly nourished. The blood pressure was 100/60. Large painful ecchymoses were noted over the right arm and the buttocks extending down to the right ankle. The fingers and toes were clubbed. Deep tendon reflexes were absent. Vibration sense was absent below the waist. Other laboratory findings pointed to a malabsorption syndrome (Table II). Bone survey revealed generalized osteoporosis. X-ray examination of the small bowel revealed a deficiency pattern from the duodenum through the terminal ileum. Pancreatic function was normal. Cerebrospinal fluid was normal. Hematological work-up revealed a prolonged prothrombin time, 128 seconds (control 12 seconds), which promptly returned to normal, 15 seconds (control 15 seconds), following injection of vitamin K. The Rumpel-Leede test was negative. The ecchymoses disappeared and the patient was discharged with massive doses of vitamin B₁₂.

The patient was readmitted in May 1951 and in July 1952 for exacerbations of the sprue syndrome. Symptomatic control was achieved with steroid therapy on both occasions.

In December 1954 he sustained a partial fracture of the left femoral neck which was treated by pinning. His neurological findings remained stationary. He is maintained on 10 milligrams of prednisone a day at the present time and weighed 127 pounds.

Comment: A middle-aged man was admitted for painful massive ecchymoses of the buttock and extremities following venipuncture and intramuscular injections. He had a history of steatorrhea and weight loss for 17 years. The diagnosis of non-tropical sprue complicated by hypoprothrombinemia was made. He had moderate osteoporosis with fracture of the left femur, and neurological findings simulating peripheral neuropathy and a typical, subacute combined degeneration. He had been symptomatically controlled on steroid therapy for five years

Case 11

M. S.*, a 73-year old man, was hospitalized in March 1941 because of melena for several days and ecchymoses over both hands. He had diarrhea with steatorrhea for two years and a history of ecchymoses. On examination he appeared emaciated and chronically ill with lemon-yellow pallor. The blood pressure was 90/60. The tongue was smooth and beefy-red. Petechiae were present on the hard palate and ecchymoses on the dorsum of both hands. There was moderate abdominal distention. Laboratory studies are presented in Table II. The prothrombin time on admission was 70 seconds (control 23 seconds). Following vitamin K therapy the prothrombin time was 23 seconds. X-rays of the gastrointestinal tract revealed a small hiatus hernia, in addition to a deficiency pattern. Osteoporosis was noted. He was treated with blood transfusions and vitamins with improvement.

He was hospitalized again in August 1944 because of severe melena and epistaxis. The prothrombin time was 120 seconds (control 30 seconds). In September 1944 hematuria and a subconjunctival hemorrhage were observed with a prothrombin time of 25 per cent. Bleeding stopped after administration of Hykinone and ascorbic acid. He was placed on a regimen of liver injections, parenteral calcium and oral vitamin B complex, vitamin C and K. He was last observed in November 1944.

Comment. An elderly man developed diarrhea and steatorrhea two years before hospitalization for melena and ecchymoses. The prolonged prothrombin time became normal after vitamin K therapy. Three years later he had severe melena, epistaxis and hematuria associated with marked hypoprothrombinemia.

Case 10

N. M., a 60-year old woman, was hospitalized in March 1941 because of swollen ankles, bleeding gums and epistaxis of three days' duration and ecchymoses on the extremities for one day. One year before she had been told she had seven gm. per cent hemoglobin and was treated with iron and vitamins. Physical examination revealed a thin, pale woman with large ecchymoses on the right arm, from the axilla to the antecubital fossa, and on the inner aspect of the right thigh. Slight pitting pretibial edema was present. Laboratory examinations are noted in Table II. The bone marrow was megaloblastic. Dark adaptation was subnormal. Bleeding time was three minutes and coagulation time 11 minutes. Fibrinogen was normal and the Rumpel-Leede test negative. Prothrombin time was prolonged to 47 and 55 seconds (control 24 and 26 seconds, respectively). X-ray of the small bowel revealed a typical deficiency pattern. The bones showed osteoporosis. A diagnosis of non-tropical sprue without diarrhea with complicating hypoprothrombinemia was made. She was given a high protein diet, intramuscular liver extract and oral vitamin K. The prothrombin time returned to normal after addition of bile salts. She was given vitamins A and D, calcium and iron and improved. She was followed in the clinic for three years in good condition, except for a transient episode of peripheral neuritis which responded to thiamine. She received liver extract sporadically. She remained in remission until her death in a home for the aged in 1951.

Comment: A 60-year old woman with a history of anemia and weight loss presented with epistaxis, bleeding gums and extensive ecchymoses of her extremities. She had a severe megaloblastic anemia. Despite absence of diarrhea, clinical and laboratory findings established the diagnosis of non-tropical sprue complicated by hypoprothrombinemia. The latter was corrected by vitamin K and bile salts. The patient remained in remission until her death ten years later.

* We should like to thank Dr. Burrill Crohn for permission to include this patient.

Case 6

I. H., a 41-year old woman, was hospitalized in July 1935 because of tibial pain for one week and edema for five weeks. She had lifelong diarrhea with five to six bowel movements daily and weakness and dyspnea for three years. She was dwarfed and extremely pale. Her temperature was 102°F., pulse 120 per minute and blood pressure 95/60. Petechiae were noted over the lower extremities. There were fundal hemorrhages. The tongue was smooth and atrophic. The liver was palpable two fingers breadth below the costal margin. The forearms were bowed. There was generalized bone tenderness. Laboratory data revealed severe anemia and hypocalcemia in association with malabsorption (Table II). Bone x-rays showed old rickets. Small bowel x-rays showed moderate distention. She was treated with liver extract, transfusions and iron. She was readmitted twice within three months for diarrhea, vomiting and weight loss associated with recurrent nosebleeds, hematemesis, bleeding gums and painful swelling of the left thigh. There was bilateral carpopedal spasm and a hematoma covering the left buttock, thigh and leg. The bleeding time was five and one-half minutes, clotting time 29 minutes, and fibrinogen level normal. She showed no response to multiple transfusions and calcium and died 12 days after the last admission. Post-mortem examination revealed multiple hemorrhages into the pleura, peritoneum, skin, mucous membranes, anterior mediastinum and renal pelvis. The intestine showed congestion of the mucosa and non-iron pigment granules in the muscularis. The liver and kidneys were fatty. The pathological findings have been presented in detail previously (17).

Comment: A 41-year old woman with a lifelong history of diarrhea was hospitalized with severe anemia and hypocalcemia and evidence of malabsorption. Petechiae were noted. She developed recurrent nosebleeds, severe hematemesis, bleeding gums and a large hematoma. There was low-grade tetany. The clotting time was prolonged. Despite multiple transfusions and massive calcium therapy bleeding persisted and the patient died.

Case 5

S. H., a 50-year old woman, was seen at the Consultation Service of this hospital in 1935 because of weakness, epistaxis and easy bruising for two months. She had four to five foul, bulky bowel movements daily, abdominal cramps and a ten pound weight loss. Physical examination revealed a thin, pale woman with marked dorsal kyphoscoliosis and protuberant abdomen. She persistently showed petechiae and ecchymoses on the extremities. She was moderately anemic and hypocalcemic. She had generalized osteoporosis. Steatorrhea, malabsorption and abnormal small bowel x-ray pattern led to the diagnosis of non-tropical sprue. The symptoms were controlled for ten years on bland diet, liver extract and calcium injections. Epistaxis and ecchymoses continued.

In August 1945 the patient noticed frank hematuria for one day and a large ecchymosis over the right knee. The stool showed a four plus guaiac reaction. Intravenous pyelogram, cystoscopic examinations and barium meal study for site of bleeding were negative. The prothrombin time was 35 seconds (control 15 seconds), and coagulation time 27 minutes. Bleeding stopped after a blood transfusion and Hykinone administration.

The patient was hospitalized in July and September 1950 with two episodes of extensive ecchymosis. Microscopic hematuria and guaiac positive stools were present. The patient had large confluent ecchymoses on all extremities and many petechial spots on the buccal mucosa. Her blood pressure was 70/40. A grade III systolic murmur was heard over the precordium. Laboratory data showed severe anemia, hypoalbuminemia and hypocalcemia (Table II). The bleeding time was six minutes and coagulation time 36 minutes, clot retraction adequate. Prothrombin time was markedly prolonged to 100 seconds (control 13 seconds). Prothrombin consumption was normal. Massive blood transfusions and large doses of vitamin K were given. Hemorrhagic manifestations subsided completely.

In December 1950, two months after cortisone therapy was instituted, she was admitted in extreme carpopedal spasm, with a serum calcium of 5.8 mg per cent.

In April 1951, an exacerbation of the sprue syndrome was precipitated by cortisone withdrawal. Microscopic hematuria, guaiac positive stools and intermittent crops of skin petechiae were observed and the prothrombin time was prolonged to over two minutes. Steroid therapy was reinstituted.

She was hospitalized for tetany following Mercuhydrin in August 1951. Skin petechiae persisted and an episode of ecchymoses involving both hands, forearms, tongue and buccal mucosa occurred in April 1952 following an exacerbation of diarrhea. Hypoprothrombinemia was again present (Table I). Steroid therapy was increased and oral vitamin K and C were added with control of symptoms.

From 1953 through 1956 the patient was maintained asymptomatic on steroid therapy with supplemental multiple vitamins and calcium.

Comment: A 50-year old woman had various hemorrhagic manifestations during 21 years of observation. Frank hematuria, epistaxis, multiple ecchymoses, petechiae, and hemorrhage into the tongue and buccal mucosa occurred repeatedly. Hypoprothrombinemia was constant. There was secondary anemia, extensive osteoporosis and hypocalcemia with tetany. After steroid therapy, only one major bleeding manifestation occurred. She has been maintained in clinical remission on a minimal dose of steroid for six years.

DISCUSSION

In 1927, Fanconi described three patients with celiac disease and a hemophilia-like hemorrhagic diathesis different from scurvy in which the clotting time was prolonged and the platelets normal (18). He later described this syndrome as resembling fatal fulminating purpura (19, 20). In 1938, he suggested that the bleeding might be caused by a deficiency of vitamin K and thereby of prothrombin (21).

Subsequently, hypoprothrombinemia was demonstrated in patients with non-tropical sprue (Table III) (3, 4). In 1940, Kark, Souter and Hayward (5) reported a patient with sprue who developed a severe hemorrhagic tendency with marked hypoprothrombinemia corrected by administration of oral synthetic vitamin K. Since then six reports of similar instances of sprue complicated by hemorrhages have appeared in the literature (6-11). Details of these patients are presented in Table III. The findings in this group of patients are similar to those in the present series as regards duration of disease, bleeding manifestations, marked hypoprothrombinemia, correction by administration of vitamin K, and association with other complications, particularly tetany.

Reviews of large series of patients with idiopathic sprue reveal the absence of bleeding and hypoprothrombinemia in patients with the tropical variety (12-14) while the incidence in non-tropical sprue is of the order of 10 to 22 per cent (2, 17). In the present series bleeding was noted in 30.5 per cent of the total group. Only two of the patients from Puerto Rico had any hemorrhagic manifestations. If these patients are excluded, the incidence of bleeding rises to 40 per cent of patients with non-tropical sprue. Massive bleeding as a prominent presenting feature occurred in 11.7 per cent of this group of patients.

The seven patients presented in detail in this study showed hemorrhagic mani-

TABLE III
Previously Reported Cases of Sprue Complicated by Bleeding

Author	Year	Age	Sex	Hemorrhagic Manifestations	Prothrombin Time (sec.)	Clotting Time	Symptoms	Therapy
Bassett et al (3)	1939	36	M	Hemarthrosis, ecchymoses, hematuria, melena	—	40'	Diarrhea, 4 yrs., tetany	Transfusions
Kantor (4)	1940	45	F	Melena	—	(prolonged)	Diarrhea, tetany	Died
Kark, Souter & Hayward (5)	1940	62	M	Purpura, hematuria, melena	96/25	20'	Diarrhea, 3 yrs., tetany	Vit. K (oral, synthetic)
Allen (6)	1941	—	F	Menorrhagia, ecchymoses, bleeding gums	(15%)	—	Diarrhea, 3 yrs., tetany	Alfalfa conc., synthetic vit. K & K ₁
Alper (7)	1942	57	F	Hemarthroses, purpura, ecchymoses	26/15	—	Pathological fractures, 7 yrs., osteoporosis, no diarrhea, steatorrhea with 39% fecal fat	—
Collins & Hoffmanns (8)	1943	—	—	Hemoptysis, hematuria	41	—	Diarrhea, 4 mos., calcium 8.3	I.V. vit. K, previous sulfa therapy
Ingelfinger (9)	1943	31	F	Hematuria, epistaxis, purpura	<1%	—	Diarrhea, 2-3 mos., tetany	—
Butler & Young (10)	1955	39	F	Recurrent ecchymoses, menometrorrhagia	>24	27'	Diarrhea, 2 wks., calcium 8.6, osteomalacia	Vit. K
Scharfman & Propp (11)	1956	53	F	Purpura, melena	>4 mins.	> 24 hrs.	Diarrhea, 4 yrs., calcium 8.0	Vit. K and blood transfusions

festations as a major complication of sprue. Three patients, cases 10, 17 and 23, did not have diarrhea during the acute episode of bleeding manifestations, but steatorrhea was present in all. Case 17 developed diarrhea after the diagnosis of sprue was established. On the other hand, case 6 had diarrhea for 41 years and case 16 had diarrhea for 17 years before developing hemorrhagic complications. Hypoprothrombinemia (vitamin K deficiency) was proven the cause of hemorrhagic manifestations in all instances except case 4 who was hospitalized prior to the discovery of vitamin K. Hypoprothrombinemia, therefore, seems to be related to malabsorption of fat rather than to diarrhea. The possibility that the sprue syndrome may be the cause of bleeding due to unexplained hypoprothrombinemia should be borne in mind even in the absence of the full-blown clinical picture of sprue.

Vitamin K is a fat-soluble vitamin which is present in certain vegetables and absorbed from the jejunum. It is also synthesized in the intestine by bacterial flora. Only small amounts are stored in the body. A very small amount is necessary to maintain plasma prothrombin above the critical level (a few micrograms) (22). Deficiency of vitamin K in sprue may be due to inadequate dietary intake (low fat diet), deficient synthesis due to alteration of intestinal flora, malabsorption from the intestine, or increased loss in the stools. Hemorrhages occur in patients whose diets have not been restricted in fat and who do not have diarrhea, suggesting that these factors are not responsible for vitamin K deficiency. The importance of alterations in intestinal flora in the etiology of the sprue syndrome has been emphasized by Frazer (23). None of the patients showed any impairment of liver function. None showed clinical jaundice. In one case that came to autopsy, case 4, the liver showed only minimal fatty changes. Prothrombin deficiency in these patients was not due to a defect in synthesis as seen in liver disease. It seems apparent, therefore, that malabsorption is the primary cause of deficiency in vitamin K.

Hypocalcemia was present in all of the seven patients. Four had manifest tetany. All except one had marked osteomalacia and one patient had sustained a pathological fracture of the femoral neck. These findings may be a reflection of deficiency of vitamin D as well as of calcium. Similar findings were noted in the patients with hemorrhagic phenomena reported by others (Table III). Of these nine patients, five had tetany, one had pathological fractures, one had osteomalacia and the remaining two had slight hypocalcemia.

Five patients had a hypochromic anemia and an erythroid bone marrow. One patient had a macrocytic anemia (case 16). Case 10 was the only patient to show a megaloblastic bone marrow. In contrast, 80 per cent of the sprue patients from Puerto Rico included in this review presented with macrocytic anemia or a megaloblastic bone marrow. Most of these patients responded favorably to liver extract intramuscularly. That megaloblastic anemia is not a necessary feature of the sprue syndrome in Puerto Rico has been demonstrated recently by Gardner (24). Therefore, in non-tropical sprue bleeding manifestations (hypoprothrombinemia) which are not too uncommon are usually associated with hypocalcemia, tetany and extensive osteoporosis. In the tropical variety, these

complications are rare and megaloblastic anemia may be a more consistent feature of the disease, at least among the usual Puerto Rican patients.

It is of interest that two of the seven patients had septicemia due to gram-negative organisms usually found in the intestine. This complication has been rarely observed in sprue.

Institution of steroid therapy in three of the seven patients resulted in a marked decrease in the incidence of hemorrhagic manifestations (cases 5, 16, 23). This is especially evident in case five who had crops of skin petechiae intermittently during 21 years of observation. Massive hemorrhages occurred three times within two years prior to the institution of steroid therapy. Only one minor episode of ecchymoses was observed in the six years during which she was maintained on minimal doses of steroids. Both patients 16 and 23, who were also on steroid therapy, had no recurrence of bleeding after the initial episode. Steroid therapy apparently improved intestinal absorption (25, 26) and thereby sufficient vitamin K was available to maintain normal plasma prothrombin levels.

SUMMARY

Eighty-two sprue patients, 27 men and 55 women, observed at The Mount Sinai Hospital from 1931 to 1956 were reviewed for incidence of hemorrhagic manifestations. Twenty-five patients, seven men and 18 women, exhibited bleeding with severe hypoprothrombinemia directly attributable to malabsorption of vitamin K. Severe skin bleeding (petechiae, ecchymoses, purpura) was most frequently observed; although epistaxis, bleeding gums, melena, hematuria, hematemesis and menorrhagia were also encountered. Seven patients, three men and four women, in whom hemorrhagic phenomena were a prominent presenting feature requiring hospitalization are reported in detail. These cases illustrate that hemorrhagic manifestations of sprue can be fulminating although the primary disease is obscure. The importance of malabsorption of vitamin K as the cause of hypoprothrombinemia in sprue is stressed and the possible role of steroid therapy in correction of this malabsorption is discussed.

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NEUROLOGIC MANIFESTATIONS IN THE MALABSORPTION SYNDROME

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In considering the neurologic manifestations of the malabsorption syndrome, we include celiac disease of children, tropical sprue and non-tropical sprue (idiopathic steatorrhea). In celiac disease of children, neurologic sequelae are not mentioned, except as rarities (1-3). With reference to tropical sprue, there is no note of neurological complications in Grodwohl's textbook on "Tropical Medicine" (4). In a paper on post-mortem findings on tropical sprue, Mackaie and Fairley (5) state that in their clinical experience there have been no signs or symptoms of central nervous system or peripheral nervous system involvement. In a hundred cases of sprue in Puerto Rico, 14 per cent were found to have numbness of the toes and fingers, formications and paresthesias, 10 per cent had decreased or absent deep tendon reflexes and decreased or absent vibration sense below the iliac crest (6). The conclusion was that in tropical sprue absence of neurological manifestations was the rule. Thaysen (7) described in his monograph on non-tropical sprue frequent occurrence of paresthesias of the hands and toes in the absence of anemia. He never was convinced of the presence of any actual disturbance of sensibilities despite some transient neurological findings such as Babinski signs and clonus. Thaysen believed that neurological abnormalities in non-tropical sprue were rare as well as inconspicuous.

This report is an analysis of the neurological manifestations in 94 cases of the malabsorption syndrome studied in the clinics and wards of The Mount Sinai Hospital for a period of years, including follow-up observations averaging seven years.

CLINICAL MATERIAL

Special studies were performed in patients 1, 2, 3, 4, 14, 15, 45 and 46, while the remainder were subjected to the routine neurological examination. Detailed case histories of the first four patients are presented.

CASE REPORTS

Case 1

A 43 year old white man was well until 1942 when he began having watery non-bloody diarrhea, vomiting, weakness and concomitant 16 pound weight loss; his bowel movements were foul smelling. He was hospitalized for six weeks with improvement. In 1945, he was admitted to another hospital for four months with recurrence of diarrhea and vomiting. In 1948, he was readmitted for similar symptoms and a spontaneous fracture of the left hip and, in 1949, for a relapse of diarrhea, extreme gaseous distension of the abdomen and pneumonia. Blood transfusions were administered at that time, as well as folic acid and vitamin B₁₂. He stayed 14 months and was discharged on liver injections and vitamin B₁₂. The patient was unable to work after 1950, and remained in a nursing home part of 1952. From November

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1952 to the time of this admission he was at a hospital where he received injections of ACTH. For about two years the patient had noticed stiffness and numbness of the extremities, inability to move his arms and legs and marked paresthesias. This progressed to a degree where he could barely walk and he could stand only when holding on to something. At this admission to The Mount Sinai Hospital (1953), diarrhea was intermittent, watery and foul-smelling. There was no vomiting and the appetite was good (his weight stabilized at 110 pounds, highest normal weight 145 pounds). The patient was raised in Italy, but has lived in New York City since age 19. There was no family history of diarrhea or pernicious anemia. He denied any parasitic infections. Past history revealed that he had had an operation for a cataract of the left eye 1948 (total amaurosis of left eye since 1942).

Physical examination in December 1953 revealed normal temperature, pulse, and respiration. The blood pressure was 90/50. The patient was an emaciated, chronically ill, white man with marked dorsal kyphoscoliosis, very short stature, who was unable to walk unassisted. The skin of the arms and face was bronze in color and there was brown spotty pigmentation of extremities. There was no vision in left eye and the left pupil did not react to light. There was brown spotty pigmentation of the lips and buccal mucosa. The tongue was pale, smooth, and presented cheilosis. The chest showed marked dorso-kyphoscoliosis and increased anterior-posterior diameter with flaring of ribs. The abdomen was distended but not tender. Bowel sounds were hypoactive.

Neurological examination: The cranial nerves were intact, except for the blind left eye and left internal strabismus. There was marked weakness of the lower extremities, mainly in the proximal musculature. The hand grip was weak. The Romberg test was positive. He was markedly ataxic with severe heel-to-knee dysfunction. The deep tendon reflexes were absent throughout. There were no pathological reflexes. Vibration sense was absent below the iliac crest; it was also absent distally below both elbows. Position sense was absent in all the toes and in the fingers of the left hand. There was impairment of position sense in the fingers of the right hand and marked astereognosis bilaterally. There was hyperpathia of the soles of the feet.

Laboratory analyses: Urine, negative, except for occasional trace of 1 plus albumin; hemoglobin, 4.75 gm. per cent; red blood cell count, 2.53 million per cu. mm.; hematocrit, 21; white blood cell count, 5700 per cu. mm.; platelets, 230,000 per cu. mm.; MCV, 83; MCH, 19; MCHC, 23; extreme hypochromia, marked anisocytosis, many macrocytes and microcytes; sedimentation rate, 30 mm. per hour (Westergren); BUN, 10 mg. per cent; CO₂, 52 vol. per cent; chloride, 105 mEq. per liter; sodium, 133 mEq. per liter; potassium, 4.8 mEq. per liter; serum protein, 6.8 gm. per cent; A/G ratio, 3.6/3.2; calcium, 5.9 mg. per cent; phosphorus, 3.5 mg. per cent; alkaline phosphatase, 24 King-Armstrong units; bilirubin, 0.2 mg. per cent; cholesterol, 93 mg. per cent, esters, 70 mg. per cent; prothrombin time, 16 seconds (control, 13 seconds); phospholipids, 93 mg. per cent; serum iron, 45 μ g. per cent; total iron binding capacity, 361 μ g. per cent; fasting carotene level, 8 μ g. per cent. Vitamin A tolerance: fasting, 16 μ g. per cent; four hours, 13; six hours, 19; eight hours, 18 μ g. per cent. Oral glucose tolerance (100 gm. glucose): fasting blood sugar, 97 mg. per cent; half hour, 104; one hour, 100; two hours, 200; three hours, 90 mg. per cent. Intravenous glucose tolerance test: half hour, 160 mg. per cent; one hour, 140; one and one-half hours, 150; two hours, 88 mg. per cent. Marrow iron tolerance test: fasting sample, 48 μ g. per cent; half hour, 43; one hour, 56; two hours, 100; three hours, 95; four hours, 150; five hours, 195; six hours, 176 μ g. per cent (impaired absorption). Gastric analysis revealed free hydrochloric acid to be present. Spinal fluid was normal. Bone marrow: normal cellularity with slight increase in megakaryocytes, many white blood cells larger in size and with more band cells than usual; many pro-erythroblasts and erythroblasts, some with atypical nucleus structure resembling megaloblasts; many normoblasts were basophilic and polychromatophilic. X-ray examinations revealed a fairly marked degree of demineralization of all bones. The right hemithorax was narrower than left. There was an old fracture of right scapula, right clavicle and lateral third rib and neck of left femur. Focal areas of atelectasis above both diaphragms were seen. Small bowel studies revealed no definite evidence of mucosal abnormality, the bowel

loops were somewhat dilated and some segmentation and irregularity of contour suggesting mucous secretion. There was tremendous dilatation of the large bowel, however the terminal ileum was normal.

The patient was started on parenteral vitamin B₁₂, 1000 micrograms daily, which he received throughout his hospital stay. A fall in hemoglobin to 3.9 gm. per cent necessitated blood transfusions. Bone marrow aspiration following an injection of 3000 micrograms of B₁₂ showed a normoblastic erythropoiesis. After approximately three weeks on B₁₂ alone, three milliliters of crude liver extract daily was added to the regimen and continued throughout hospitalization. Despite vitamin B₁₂, liver extract and transfusions, the patient's hemoglobin which had risen to 8.7 gm. per cent, fell to 5.8. Following radioactive iron studies, the patient was started on a course of intravenous iron totalling two grams over the course of 20 days. At its completion, the hemoglobin had risen to 11.9 gm. per cent with a concomitant feeling of well being. At this point, the following studies were repeated and showed no change from those on admission: glucose tolerance test, vitamin A tolerance test, small bowel x rays; serum cholesterol rose to 122 mg. per cent, esters to 87 mg. per cent and phospholipids to 151 mg. per cent. There was no change in the neurologic status. The patient was then started on physiotherapy which continued throughout hospitalization. He had gained 14 pounds to this point, but the diarrhea persisted intermittently along with abdominal distension. After six weeks of physiotherapy, the patient was able to walk unaided with crutches and the range of motion had increased in the involved joints. The patient was started on hydrocortisone, 80 mg. daily. He felt stronger and his bowel movements decreased to one daily. Hydrocortisone was then reduced to 60 mg. daily. After six weeks on hydrocortisone a vitamin A tolerance test was still flat and it was noted that the patient's hemoglobin had fallen again to a level of 8.4 gm. per cent; therefore, a second course of intravenous iron was given, again totalling two grams, with a rise in hemoglobin to a level of 12 gm. per cent. Blood studies then revealed red blood cell count, 5.15 million per cu. mm.; hematocrit, 45.5; MCV, 88; MCH, 23; MCHC, 26. Re evaluation of the neurological status prior to discharge showed no evidence of improvement or progression. Repeat small bowel x-ray at that time showed normal transit time and considerable change in the appearance of the small bowel as compared with previous films. Dilatation was less marked and the increase in secretion probably present was to a much lesser degree than previously noted. The evidence of late segmentation was also less pronounced. Serum cholesterol had risen to 215 mg. per cent.

The patient was then transferred to a chronic disease hospital where he was seen in the summer of 1956 and gave a history with respect to his neurological symptoms as follows: for six or seven years there had been numbness (pins and needles sensations) of the right hand which then spread to involve the left hand and eventually both lower extremities. He described the feelings also as stiffness and tightness. In 1952, he developed further numbness of the feet and began to have progressive difficulty in walking and within a short time became completely dependent upon a wheelchair. There were no other neurological symptoms, including no difficulty in urination or defecation.

On neurologic examination he was alert, cooperative and showed no evidence of an organic mental syndrome. Cranial nerves were intact, except for blindness in the left eye, apparently due to fibrous scarring of the cornea. There was also an internal strabismus of the left eye. Motor examination revealed marked atrophy of all extremities, especially in the intrinsic muscles of the hands. In addition to generalized weakness, he could not walk. The Romberg sign was markedly positive. Heel to knee test was done very poorly with the eyes closed and open. There was finger-to-nose ataxia with the eyes closed, but less ataxia with the eyes open. Biceps, triceps, knee and ankle reflexes were all absent. There were no Babinski signs. There was hypoalgesia of both hands and the lower third of the forearm. There was no impairment of pin sensation in the lower extremities. Touch was impaired in the entire body except the face. Position sense was absent in the toes and was markedly impaired in all the digits of the hands. There was bilateral astereognosis. Vibration sense was decreased in both iliac crests and below. Vibration sense was present in the elbows

but was decreased in both wrists and hands. In general, there was not much change in his neurological picture since 1953. During the stay at the chronic disease institution, he had been maintained on high protein, low fat, simple carbohydrate diet; vitamin A in doses of 50,000 units a day; calcium lactate 15 grams three times a day; parenteral liver injections weekly; vitamin B₁₂, 50 micrograms weekly and cortisone 25 mg. daily.

Comment: This 45-year old man suffered from the malabsorption syndrome for 15 years. The course has been a stormy one with seven admissions for exacerbations of the gastrointestinal symptoms. He became anemic to the point where he required blood transfusions and also developed pathological fractures due to hypocalcemia. Ten years after the onset of his illness, there ensued a neurological syndrome primarily a myeloradiculo-neuropathy which progressed, despite vigorous therapy with vitamin B₁₂ and liver extract, to a point where he was totally incapacitated. He has been maintained on vitamin B₁₂, liver extract and cortisone and has even received a course of folic acid. Nevertheless, there has been no change in his neurological status during the past three years.

Case 2

A 46 year old white woman was admitted for diagnosis and therapy in 1954. Her illness actually extended to infancy, when she had abdominal distension, diarrhea, frequent episodes of vomiting, nausea, fever and respiratory infections. She recalled, as a child, that her mother prepared many special foods for her and remembered eating many bananas. There was a decrease in symptoms until the age of 28 when she had a rather marked exacerbation of her diarrhea and abdominal pain, associated with anemia. In 1945, she was started on liver injections for her anemia and thereafter improved somewhat. She was hospitalized for about one month in 1946 for abdominal distension, diarrhea, severe weakness, anemia and a severe productive cough. Although she was suspected of having tuberculosis at this time, it was never substantiated. In December 1950, she was admitted to another hospital where her presenting complaints were again diarrhea, weakness and weight loss. She had an anemia with a prolonged bleeding time (40 seconds) but normal clotting time; her stools were bulky and foul smelling with a high fat content; oral and intravenous glucose tolerance tests were normal; calcium was 10.8 mg. per cent; serum protein was 5.9 gm. per cent; and she had free hydrochloric acid in her gastric contents. Gastrointestinal series at that time showed "fragmentation of the barium meal." She was treated successfully with vitamin B₁₂, folic acid and crude liver injections. In the summer of 1952, she developed ankle edema and an exacerbation of diarrhea, abdominal distension and pain. She was again admitted and was found to have a flat glucose tolerance curve, a persistent anemia, a hypoproteinemia and again an altered mucosal pattern of the small bowel. She complained of paresthesias of the hands and feet and, although she noted twitching of her fingers, the blood calcium was normal. She had minimal evidences of purpura. She was again treated and did well until February 1953 when, following an episode of "grippe", she was readmitted weighing 80 pounds. During this hospitalization, her calcium was noted to be 8.4 mg. per cent with a normal phosphorus; sigmoidoscopy was negative. She was started on cortisone and maintained on 25 mg. daily. In addition, she received 25 mg. of folic acid daily and crude liver extract, 1 ml. daily. She was also treated with calcium; vitamins A, D and K; and a high protein, simple carbohydrate, low fat diet.

Physical examination revealed a thin, poorly nourished woman with scrawny limbs, a distended abdomen, looking for all the world like a grown-up celiac. There were no pigmentations, no ecchymoses, no eye-ground changes or abnormalities of the tongue. She had no cheilosis. The abdomen was distended and tympanitic. She had 2 plus pitting edema of the lower extremities without sacral edema. She had no clubbing, joint pain or bony tender-

ness. Neurological examination was unremarkable. She had no Trousseau or Chvostek signs. Tourniquet test was negative. Fluoroscopy revealed no abnormalities of her heart or lungs.

Laboratory analyses: Hemoglobin, 10.9 gm. per cent; hematocrit, 47; RBC³, 4.75 million per cu. mm.; MCV, 98; MCH 27; MCHC, 27; platelets, 210,000 per cu. mm.; reticulocytes, 0.6 per cent; white blood cells, 6400 per cu. mm. with 40 per cent segmented polys, 30 per cent lymphocytes, 3 per cent eosinophiles, and 16 per cent monocytes. The blood findings indicated a slight hypochromic but normocytic anemia. Urine examination, sedimentation rate, BUN, fasting blood sugar, plasma carbon dioxide, chloride, sodium, potassium, calcium and phosphorus were normal. Serum protein was 5.69 gm. per cent and the A/G ratio was 2.7:2.4. The prothrombin time was 12.5 seconds (control, 12.5 seconds). Bone marrow examination showed a cellular marrow with an adequate number of megakaryocytes, a marked eosinophilia and normoblastosis, consistent with the recovery phase of a megaloblastic anemia treated with B₁₂ or folic acid. Stools were bulky and foul smelling with a high fat content. Serum mucoproteins were 56.6 mg. per cent, polysaccharide of total serum protein was 86 mg. per cent and the polysaccharide mucoprotein ratio was 1.5, all of which were within normal range. Enteric agglutinins were all negative. Oral glucose tolerance test showed a flat curve with no glycosuria. Stool culture revealed *B. coli* and *A. aerogenes*. Vitamin A tolerance test was extremely low with an indeterminable carotene level. Serum cholesterol was 105 mg. per cent; cholesterol esters, 86 mg. per cent. Duodenal drainage with a secretin test showed normal pancreatic function. X-ray of the chest was normal. Barium enema examination showed no abnormality in the esophagus or the stomach. The duodenal bulb was normal except that it appeared somewhat enlarged with thick but regular mucosal folds. The small bowel showed considerable coarsening of the mucosal pattern with moderate dilatation of the lumen, slight segmentation and marked flocculation. Transit time was not grossly disturbed. The changes described were consistent with the clinical diagnosis of non-tropical sprue. Oral cholecystography showed good filling and emptying of the gall bladder with no stones. Skeletal survey revealed a moderated demineralization of visualized bone with no evidence of pseudo-fractures. Calcific densities were noted posterior to the pineal in the skull and probably represented calcification in the choroid plexuses.

The patient had as many as six fatty, foul smelling stools a day. She was started on crude liver extract, menadione, 30 mg. daily of folic acid, vitamin B₁₂ (50 micrograms daily), and a high protein, high caloric, low fat diet. On the twenty-second hospital day, she was started on 80 mg. of hydrocortisone daily which was reduced to 60 mg. after one week, but had to be raised since she had an episode of watery diarrhea. This was finally decreased to 40 mg. daily. She was discharged after a hospital stay of six weeks on 30 mg. of folic acid twice weekly, 50 mg. of vitamin B₁₂ intravenously, 9 grams of potassium chloride four times a week and supplementary feedings rich in protein. Because of subsequent gastrointestinal symptoms, she was given cortisone. It was felt that her neurological symptoms became worse and when the corticosteroid therapy was discontinued her neurological manifestations improved. A later relapse of sprue necessitated resumption of steroid therapy and it was then given in combination with massive parenteral doses of liver extract and vitamin B₁₂.

On October 18, 1955 she gave a history of a gradual onset of tingling of the hands and the feet since 1951. There were occasional cramps of the toes. These symptoms became less marked but in September 1955, she began to have difficulty in feeling objects, such as buttons and money in her pocket and this had become worse in spite of treatment. She also stated that at times she had burned her fingers and on one occasion a nail in her shoe pierced her foot, but she did not feel it and only later she noticed blood on her stocking. There was also a feeling of not having any sensation about the mouth, and difficulty in tasting things with the tip of her tongue. Her mouth had become very dry and so had the skin of the fingers and soles of the feet. She also mentioned having had dizzy spells which consisted of feelings of being giddy or faint and usually occurred when sitting up rapidly. She com-

plained of urinary frequency and stated that it was uncomfortable to postpone going to the bathroom.

The cranial nerves were entirely intact, except that there was decreased pin sensation throughout the distribution of the trigeminal nerve bilaterally. The tongue appeared smooth. There was no hypoalgesia of the tongue or other mucous membranes. The gait was normal and the Romberg test was negative. There were no abnormal movements. Motor power and tone were normal. There were no fasciculations or atrophy. Finger-to-nose test was done relatively well, but finger-to-finger performance was poor. Heel-to-knee testing was normal. Alternating and discrete fine movements were normal. The biceps, triceps and knee reflexes were all decreased on the left. There were no pathological reflexes. There was decreased sensation to cotton in all the fingers extending to the wrist and all the toes to the ankle. There was position sense loss in the fingers, most marked in the second and third fingers on the right and the second to fifth fingers on the left. There was bilateral astereognosis. Vibratory sense was absent in all her toes except the right big toe and decreased below the ankles. There was a hypoalgesia in the hands and feet. Heat sensation was diminished in the fingers and toes. Two point discrimination was markedly impaired in all digits. There was no extinction or displacement on bilateral spontaneous stimulation.

Comment: This 46 year old woman was particularly interesting because she had apparently had celiac disease in childhood and suffered almost continually from diarrhea. Today, she is a typical adult case of the malabsorption syndrome. Approximately 30 years after the onset of her illness, she developed neurological symptoms in spite of vitamin B₁₂, folic acid and liver extract. The syndrome was mainly that of posterior column involvement and was probably a myelo-radiculoneuropathy. When she was given cortisone, there was a relapse of symptoms but this remitted with discontinuance of the hormones. However, later on, corticosteroids were needed because of the gastrointestinal condition and she was given cortisone concomitantly with massive doses of liver extract and vitamin B₁₂ which seemed to have protected her from further neurologic damage.

Case 3

A 49 year old man had a history of intermittently recurrent diarrhea for the past eight years. The stools were unformed and foamy, occurring one to two times daily. He was hospitalized in 1936 because of sores on his tongue, one at the tip and another on the left side. These persisted and interfered markedly with his sense of taste. The day after the appearance of these, he developed a severe "rheumatic" pain in the right upper arm and shoulder which gradually spread in the course of three or four days across his upper back to his left shoulder. There was no swelling or limitation of motion. The pain, had, on many occasions, awakened him from sleep. At the same time he began to have a sensation of a cold collar inserted at the base of his neck. This, too, had persisted with some remissions at the time of admission. At night he had experienced severe burning in both hands. For the past week, he complained of numbness in both hands and a lack of a sense of touch. On one occasion, he reached for a coin in his pocket and, thinking he held one, tried to pay for his shine to be surprised when he was told there was no coin in his hand. On many occasions he dropped things because he could not feel them in his grasp. He had not burned his fingers inadvertently. His gait had been steady. There had been no abdominal pain, girdle pain in the abdomen, headache, stiff neck, vomiting, or other neurological symptoms.

He was told he had syphilis six years prior to admission (blood serology was positive on a hospital admission for myocardial infarction). He was treated for one year with weekly injections.

General physical examination revealed a thin, chronically ill, irritable, truculent individual who tended to take offense on unintentional slights. The sensorium was clear. There

was bilaterally ptosis of the lids. The right pupil was slightly larger than the left; both reacted to light, the left better than the right. Fundi and visual fields were normal. There was a right central facial weakness. There was slight thickness and slurring of speech. He stumbled over test phrases. Motor power was reduced in both grips, but fair in the proximal segments of the arm. Power in the lower extremities was good. There was slight finger-to-nose ataxia bilaterally, and more marked finger-to-finger ataxia. There was no heel-to-knee ataxia. The deep tendon reflexes in the lower extremities were absent. In the upper extremities, the pectoral reflexes were active, but biceps and triceps reflexes were absent. There were no pathological reflexes. The abdominal reflexes were absent. There was a zone of skin hyperesthesia and hyperalgesia over the C_3 - C_5 segments on both sides; most marked about C_4 segment. There was a subjective feeling of tightness associated with spontaneous pains over these zones. There was bilateral astereognosis in the hands; defective joint sense in the fingers. Vibration was absent in the fingers; diminished in the wrist and elbows; markedly impaired in the right toes, less so on the left; slightly diminished above the shins.

Laboratory analyses: hemoglobin, 8.5 gm. per cent; white blood cell count, 4800 per cu. mm.; segmented polys, 53 per cent; lymphocytes, 53 per cent; monocytes, 5 per cent; plasma cells, 1 per cent; eosinophils, 6 per cent; phosphorus, 4.1 mg. per cent; calcium, 12.5 mg. per cent; Wasserman, negative. Janney test: blood sugar #1, 90 mg. per cent; #2, 105; #3, 95; #4, 85; #5, 85 mg. per cent. The spinal fluid was clear and colorless; initial pressure, 80 mm. water; there was no evidence of block; there were three cells per cu. mm.; total protein, 50 mg. per cent; spinal fluid serology (Wassermann) and colloidal gold were negative. A repeat spinal fluid examination revealed a total protein of 81 mg. per cent and the colloidal gold test was still negative, as was the serology test. Gastric analysis revealed free hydrochloric acid. X-rays of the cervical and dorsal spine showed no abnormalities.

It was thought that the patient was suffering from a radiculoneuropathy most likely due to a metabolic disorder such as sprue, but possibly complicated by an old luetic infection. As a result, he was treated with both bismuth and hyperthermia as well as vitamin C in injections. He was discharged unimproved.

Comment: This was a 49 year old man who developed neurological signs and symptoms after 18 years of intermittent diarrhea. The picture was complicated by a history of syphilis discovered six years prior to the onset of neurological manifestations. On admission, blood and spinal fluid serology were negative, but the spinal fluid protein was somewhat elevated. He presented the picture of a postero-column syndrome with root pains as well as some dysarthria. There were no Argyll-Robertson pupils. He was treated with heavy metals and hyperthermia but did not respond well. He was discharged unimproved. This case dates back 20 years and it is not known what would have happened if he had been given massive doses of liver extract, vitamin B_{12} and folic acid.

Case 4

A 57 year old man, whose chief complaint was weakness and pain in the left lower extremity of eight months duration, was admitted to The Mount Sinai Hospital in 1953. He had a 25 year history of non-tropical sprue. The patient was in the Navy in World War I, travelling all over Europe, but never in tropical areas. His illness began with the gradual onset of loose stools which were liquid, foul, tan, greasy and frothy. Usually, he had two to four bowel movements per day, but had had as many as 20 per day. He had been in innumerable hospitals and had been diagnosed as suffering from mucous colitis until 1944 when a diagnosis of non-tropical sprue was made. He had been treated with folic acid, vitamin B_{12} and cortisone and had been in relatively good health, but over the long course of his illness he developed a marked generalized osteoporosis, resulting in a severe scoliosis. He had no melena, tenesmus, abdominal pain or eructation, but passed much flatus. During

the first few years, he fell from his average weight of 154 to 110 pounds, which had been maintained while on a normal diet, except for a low fat content. However, in 1948, he spontaneously developed several large, painful ecchymoses and hematomas over the buttocks, thighs and ankles. At that time he was described as poorly developed, older than his stated years, looking slightly icteric, with marked clubbing, pallor and a distended tympanitic abdomen. He had massive ecchymoses over the lower half of the body. The Chvostek, Trousseau and tourniquet tests were all negative. Laboratory workup revealed the hemoglobin concentration to be 9.9 gm. per cent, the white blood cell count and urine were negative. Platelet count was 190,000 per cu. mm. Vitamin K therapy was started in massive doses and three days later the prothrombin time was 15 seconds (control 15 seconds). Oral glucose tolerance and vitamin A tolerance tests revealed flat curves. The carotene level was 9 μ g. per cent, which is strikingly low. Serum protein concentration was 5.3 gm. per cent and the A/G ratio was 3.1/1.4.

On a low fat, high protein diet and vitamin K, he improved quickly and was discharged. He was put on massive doses of vitamin B₁₂ and was maintained on 25 micrograms three times a day by mouth. His diet was essentially a low fat one with occasional vitamin B supplements. There were no recurrences of bleeding. His bowel movements varied in frequency from two to four per day. For 13 years prior to admission he had had difficulty in walking, especially up stairs. He had a limp which he attributed to "weakness" which on further questioning was a sharp electric pain in the small of his back when he flexed his leg at the hip.

Physical examination revealed a small thin but pot-bellied white man in no distress. There was obvious marked clubbing of the fingers and toes. His height was 60½ inches, though he claims formerly to have been 62 inches tall. The remainder of the examination was not remarkable except for a distended, soft, doughy, pot-bellied abdomen.

The mental status was normal. There were no cranial nerve abnormalities. He walked with a limp, favoring his left hip and with minimal flexion at the hip. There was weakness of the proximal portion of the left lower extremity. There was weakness of extension, abduction and flexion of the left hip which was accompanied by limitation in passive movements of the hip. Both active and passive movements were painful except for extension at the hip. Neither ankle nor knee reflexes could be elicited, but there were no pathological reflexes. There was slight impairment of vibration sense below L₁ and in the upper extremities.

Laboratory analyses: Hemoglobin ranged between 11-13 gm. per cent; white blood cell count and differential were normal; the urine was negative, except for a trace of albumin; sedimentation rate, 32; BUN, 14 mg. per cent; serum protein, 7 gm. per cent with normal albumin-globulin ratio; calcium, 9.1 mg. per cent; phosphorus, 9.2 mg. per cent; total cholesterol, 117 mg. per cent; prothrombin time, 12 seconds (control, 11 seconds); cephalin flocculation, 1 plus; alkaline phosphatase, 28 King-Armstrong units; stool guaiac examinations were repeatedly negative; pancreatic function studies revealed normal pancreatic function. Gastric analysis revealed a free acid of 40 units and total acid of 75 units after a test meal of alcohol. An oral glucose tolerance test curve was absolutely flat; however, the intravenous glucose tolerance test was normal. A vitamin A tolerance test after intravenous ACTH remained flat. Small bowel series revealed a so-called "deficiency pattern," i.e., from the duodenum to the terminal ileum, the small bowel was dilated with thickened plicae, and fragmentation and segmentation of the barium column. There was no delay in transit time. Spinal fluid was clear and colorless and contained 23 mg. per cent protein and no cells. X-ray of the spine showed compression of the body of the second lumbar vertebra and to a lesser extent the remainder of the lumbar vertebra. There was generalized osteoporosis of the spine and a moderate coxa vara deformity. Because of the progressive story of weakness and the neurological findings it was thought advisable to rule out a lesion of the spinal cord by myelography. A Pantopaque myelogram revealed no evidence of obstruction to the cephalad flow up to the level of the clivus and there was no defect in the Pantopaque column.

Subsequently it was thought that perhaps disease of the hip might be the cause of the weakness and the pain. X-ray pictures of the pelvis revealed a dehiscence through the neck of the left femur which was probably due to osteoporosis and could explain the weakness and the pain. The orthopedic surgeons were consulted and their recommendation was that internal fixation of the neck of the left femur by a bolt was indicated. The patient agreed to undergo operation and has done well since surgery.

Comment: This was a 57 year old man with a 25 year history of gastrointestinal disease most likely due to malabsorption syndrome. He had done rather well on vitamin B₁₂, folic acid and cortisone for many years. He was most interesting in that he developed symptoms of weakness and pain in the left lower extremity which were believed to be due to spinal cord disease, but actually were caused by another complication of the malabsorption syndrome, namely, osteoporosis with a complicating pathological fracture of the neck of the femur. Following surgery, he did well.

OTHER CASES

Table I is a compilation of neurologic manifestations of the remaining 45 patients. These manifestations fall into three groups. Group A includes patients with neurologic signs and symptoms such as paresthesias, reflex changes and/or sensory abnormalities (21 patients). Group B is comprised of those with manifestations of tetany (16 patients). Group C is made up of patients with combined forms of both neurologic abnormalities and tetany (8 patients).

In Group A there were 21 patients with some neurologic involvement. Thirteen had complaints of paresthesias of the fingers and toes. These were described as numbness, pin and needles sensation and or burning feeling. None had objective neurological findings. Their ages ranged from 24 to 60; the duration of illness, from one to 25 years. Nine patients had severe anemia, but five had normal blood counts (one patient's blood count was not available). One of the 13 patients was said to be a possible diabetic and should be perhaps excluded from this series. Moreover, two were reported to have positive serologic tests for syphilis. An additional four patients had no neurologic symptoms, but had decreased or absent deep tendon reflexes of the lower extremities. One of these patients also had a positive serological test for syphilis. Another patient had a "cerebrovascular accident" at the age of 57 and should be omitted since this is most likely not related to the malabsorption syndrome. There were three additional patients who had both sensory symptoms and objective neurologic findings. One of these, a 65 year old man, had had bowel dysfunction for three years, was reported to have 6 gm. per cent hemoglobin and 2.2 million red blood cells per cu. mm.; another was a 37 year old man who suffered from gastro-intestinal symptoms for one year and had a normal blood count and hemoglobin; the third patient is the only one who had definite spinal cord disease in that she developed a Brown-Sequard syndrome which spontaneously cleared in a few weeks. Details were not available and it is possible that there might have been a coincidental occurrence of an acute attack of multiple sclerosis.

In Group B there were 16 patients who had tetany or signs of nerve irritabil-

TABLE I

Patient No.	Sex	Age	Duration Malabsorption Syndrome, Years	Anemia	Paresthesias	Reflex and/or Sensory Changes	Tetany
Group A 6	M	18	21	None	Present	None	None
9	F	47	2	Present	Present	None*	None
11	M	26	1	Present	Present	None	None
12	M	65	3	Present	Present	Present	None
18	F	47	4	Present	None	Present	None
20	M	49	2	Present	None	Present*	None
23	F	60	1	Unknown	Present	None	None
24	F	55	1	Present	Present	None	None
26	F	22	1	Present	Present	None*	None
27	F	24	1	Present	Present	None	None
28	F	37	1	None	Present	Present	None
33	M	34	4	None	None	Present	None
38	M	57	2	None	Present	None†	None
40	F	77	6	Present	None	Present	None
42	M	21	13	Present	None	Present‡	None
43	F	40	25	Present	Present	None	None
44	M	72	17	Present	Present	None	None
46	F	48	6	Present	Present	None	None
47	M	28	1½	None	Present	None	None
48	F	45	28	None	Present	None	None
5	F	28	17	Present	Present	Present	None
Group B 7	M	50	2	Present	None	None	Present
8	M	16	1	None	None	None	Present
10	F	55	13	Present	None	None	Present
16	M	56	1	None	None	None	Present
17	F	34	1	None	None	None	Present
21	M	45	2	None	None	None	Present
22	F	28	1	None	None	None	Present
25	F	68	15	None	None	None	Present
29	F	68	3	None	None	None	Present
30	F	37	1	None	None	None	Present
31	F	60	1¼	Present	None	None	Present
32	F	65	3	None	None	None	Present
34	F	30	10	Unknown	None	None	Present
35	F	41	19	Present	None	None	Present
37	F	42	12	Present	None	None	Present
49	F	59	3¼	None	None	None	Present
Group C 13	F	55	3	Present	None	Present	Present
14	F	47	11	None	Present	None	Present
15	F	34	12	None	Present	None	Present
19	F	28	3	Present	None	Present	Present
36	F	32	4	Present	Present	None	Present
39	F	59	3	Present	None	Present	Present
41	F	47	11	Present	None	Present	Present
45	F	42	16	Present	Present	None	Present

* Positive serological test for syphilis.

† Co-existent diabetes.

‡ Patient had cerebral lesion due to vascular disease.

ity (carpopedal spasm or positive Chvostek and Trousseau signs). Their ages ranged from 16 to 68. One patient had been ill for only three months and the patient who had been ill the longest time suffered for 19 years. None had any other manifestations of abnormalities of the peripheral or central nervous system.

Group C consisted of 8 patients, all of whom had tetany and half of whom had neurologic symptoms; the remaining four had decreased or absent deep tendon reflexes of the lower extremities. Two patients were found to have diminished sensation to vibration also and one patient had a hypoalgesia and loss of position sense of the toes. These patients were between the ages of 28 and 59 and had been ill from three to 16 years. All but two of them had a severe anemia.

DISCUSSION

The studies reported in this paper indicate that neurologic manifestations are not too rare in the malabsorption syndrome. This is in contradistinction to most writers on the subject. Thaysen (7) had mentioned paresthesias and slight but rare objective changes and was convinced that neurologic abnormalities were not conspicuous. He took strong issue with Reed and Ash (8) and Reed and Wyckoff (9), who collected cases of "atypical sprue" with neurologic complications and who felt that sprue, Addison's anemia and subacute combined degeneration of the cord were expressions of the same disease. In the latter's patients, paresthesias, sensory disturbances and reflex changes were present, and there seems to be no doubt of a peripheral radicular neuropathy, although myelopathy may be questioned. Snell (10) reported the experiences of the Mayo Clinic and described 32 cases, three of whom were considered to have subacute degeneration of the cord. Spies (11) in appraising the results of vitamin B₁₂ therapy in tropical sprue mentioned three cases with combined system disease; two of them responded to B₁₂ and a third to liver extract. However, there were no detailed reports of any of these cases. Manson-Bahr (12) stated that in severe anemia neurological symptoms such as paresthesia (tingling and numbness) were frequently seen; serious diseases of the nervous system were absent in contradistinction to Addisonian anemia. However, there was mention of a patient with paresthesias, ataxia, loss of ankle and knee reflexes which improved with vitamin B₁ injections and there were two additional cases of subacute combined degeneration of the cord accompanying a sprue anemia, one of whom ran an acute rapidly progressive course and proved to be terminal. Cord symptoms manifested themselves in ataxia of the limbs, ankle clonus and positive Babinski signs. In contrast, Lindsay (13) reported a 15 year follow-up in 37 cases of non-tropical sprue with no mention of neurologic involvement. In 1947, Adlersberg and Schein (14) reported on the clinical and pathological observations in a group of 40 patients manifesting the sprue syndrome. In this series, outspoken organic disease of the central nervous system was not encountered. The paresthetic phenomenon could always be ascribed to the anemia. Neuromuscular hyperirritability could likewise be explained in every instance by hypocalcemia. In a symposium on sprue at the Second International Congress of Internal Medicine in London, 1952, there was no mention of any serious neurological disorders

although there was passing reference to symptoms of vitamin B deficiency. Cooke, Penney and Hawkes (15) reviewed 100 cases of idiopathic steatorrhea and reported only two cases of absent reflexes, abnormal plantar response and absent vibration sense. A few patients had diminished reflexes which appeared to be the result of electrolyte disturbances rather than manifestations of peripheral neuritis; these signs disappeared with the improvement of the general condition of the patients. Davidson and Girdwood (16) in reporting the effect of folic acid on six patients, described two who had idiopathic "diarrhea." Their case 4 presented no neurologic symptoms until she was given 20 mg. of folic acid for 20 days. The patient then began to feel pins and needles in both arms and legs. At this time, the red cell count was four million cells per cu. mm. Folic acid was discontinued, but the paresthesias became worse; 14 days later, power was lost in the arms and legs, and the ankle reflexes were weak. Triceps and brachioradialis reflexes were absent. The biceps reflex was normal as well as the plantar response. There was a distal hyperalgesia in the legs, more so than in the arms and there was a tactile hypoalgesia in the lateral aspects of the lower two-thirds of both legs. The patient was given liver extract, thiamine, riboflavin and nicotinic acid with improvement of the neurological signs. Their case 3, age 61, had been successfully treated with folic acid six months previously for a severe megaloblastic anemia. For an additional four months she was well without therapy, but then developed paresthesias of the hands and the feet, ataxia, diarrhea and a blood count of four million (previously five million) per cu. mm. There was muscular weakness and wasting, hyperalgesia on pressure of muscles and nerve trunks and loss of reflexes in both arms and legs. There was pronounced impairment of fat absorption. Folic acid and thiamine did not help over a five month period and the patient progressed to profound weakness with complete loss of all deep tendon reflexes, severe sensory loss and ataxia. At no time was an extensor plantar response found and the red cell count never fell below four million per cu. mm. They then administered parenteral liver injections and the patient had a good remission.

In the first mentioned case, folic acid may have temporarily worsened the neurological condition; in the second case, it did not help, but may have perpetuated the abnormality. In our own case 1, the neurologic problems began prior to any folic acid administration and were not made worse when this substance was given. Adlersberg (17) in previously discussing this case mentioned that folic acid medication was contraindicated in idiopathic sprue in the presence of lesions of the central nervous system. He felt that increased doses of concentrated liver extract and vitamin B₁₂ and improvement of the general condition may lead to regression and disappearance of the mild manifestations of neuropathy. The severe pseudotabes of this particular patient, however, was irreversible despite marked improvement of his general status after daily parenteral administration of very large doses of concentrated liver extract, vitamin B₁₂ and iron. This patient dramatically demonstrates that although most of the neurologic manifestations in the malabsorption syndrome are minor and are related to anemia, a progressively crippling myeloradiculoneuropathy (a pseudotabes)

can ensue which is refractory to all known medication. This man has not walked in five years and is institutionalized at a hospital for chronic disease. This is a challenging problem since we do not know what factors determine which patient will develop disabling neurologic sequelae. It does not seem to be related to the duration of illness, the age of onset, the presence of tetany or the severity of the anemia.

Excluding patient 3 who had syphilis, this patient and patient 2 are the only two out of 94 patients with severe neurologic impairment. There is a possibility that they suffered from two neurologic entities not related to the malabsorption syndrome, and that the relationship is coincidental. Until we learn more about the pathophysiology of the malabsorption syndrome, especially with regard to its effect on the nervous system, this conservative attitude is advisable. At this time we can only assume a causal relationship between the malabsorption syndrome and the neurologic manifestations.

A major question which cannot be resolved is the effect of an anemia on neurologic manifestations. According to our cases, the paresthesias, diminished to absent reflexes, and the sensory abnormalities seem related to low blood hemoglobin and cell counts. However, it was not possible to correlate the neurologic abnormalities with the time, duration or severity of the anemia. Nevertheless, we have eight patients with neurologic abnormalities but normal blood values (Thaysen (7) also mentioned normal values in patients with paresthesias). These cases might indicate a malabsorption of some factor or factors which are essential for intactness of nerve tissue. Three of our cases reported in detail had periods of anemia, but the fourth was never anemic. It is true that this latter case is complicated by a past history of syphilis. However, the syphilis was treated, apparently adequately, since on the admission described there was no laboratory evidence of lues. One wonders, however, if such an illness as syphilis might predispose the development of neurologic sequelae if a malabsorption syndrome ensues.

The effect of corticosteroid therapy on the gastro-intestinal manifestations of the malabsorption syndrome has been quite gratifying. Concerning neurologic sequelae, it was felt in our case 2 that these signs and symptoms had become worse. Adlersberg (17) had previously mentioned that degenerative neurologic manifestations, not too frequently encountered in sprue, were enhanced by corticosteroid therapy and were improved by its discontinuance. Complete relapse of sprue necessitated resumption of steroid therapy. It was then given in combination with massive parenteral doses of liver extract and vitamin B₁₂ (a procedure which is now used in all patients with central nervous system involvement requiring corticosteroid therapy). This patient (our case 2) is particularly interesting because it is the only example we have of a case of celiac disease in childhood progressing to the full blown adult picture of the malabsorption syndrome who, in addition, has developed marked neurologic involvement. At present, her neurologic status is quiescent although she is currently being given small doses of corticosteroids as well as massive doses of vitamin B₁₂. We do not feel that corticosteroids are too dangerous with respect to neurologic manifestations

in patients with a malabsorption syndrome, since we have 28 other patients who take steroids and who have never developed any neurologic abnormalities. Moreover, ACTH has been given to patients suffering from the so-called Guillan-Barre syndrome (18) with perhaps some benefit in the early cases. Also, steroids have been advocated in Bell's palsy (19) and are considered to be efficacious in this particular neuropathy. At any rate, it does not seem that steroids can significantly complicate the neurologic picture.

Of the 49 cases presented, 27 had manifestations of nerve irritability, most likely due to decreased serum calcium because of malabsorption. This has been well discussed in the literature. Eleven of our cases had both objective nervous system abnormalities and tetany. It was felt that these cases showed two separate phenomena, since when tetany occurs in other conditions, definite objective sensory phenomena or reflex changes are rarely, if ever, found (20). Interestingly, the remaining 38 patients had either tetany or some other neurologic manifestation. It was not possible to explain this apparent mutual exclusion. Moreover, there was one patient in our series who entered the hospital seriously ill with tetany, who had a convulsion and died. An almost identical case was described by Pessera (21) and in his particular patient there were no pathologic changes in the brain.

THERAPEUTIC ASPECTS

Anemia. The treatment of the patient with macrocytic anemia is high doses of vitamin B₁₂, up to 1000 micrograms two or three times a week or even daily. However, if there is a microcytic anemia, iron by mouth or, if necessary, intravenously is administered; and also blood transfusions, if indicated.

Tetany. The management of tetany consists of oral doses of calcium lactate or calcium gluconate. We usually administer 15 grains three times a day. Ammonium chloride also has been found to be efficacious.

Even if the patient does not present evidence of anemia, we nevertheless maintain him on adequate doses of vitamin B₁₂. Whether one should give folic acid or not is a rather controversial subject. However, it is our impression that this substance might be helpful; but, if it is to be given, it should be done with concomitant high doses of vitamin B₁₂ and thiamine.

Corticosteroids may be indicated in the general treatment of the malabsorption syndrome and, if a patient is developing early signs and symptoms of neurological involvement, we feel that they ought to be given in combination with massive parenteral doses of liver extract and vitamin B₁₂.

SUMMARY AND CONCLUSIONS

A study of the neurologic manifestations of the malabsorption syndrome in 94 patients is presented. Forty-nine patients (52 per cent) had signs and symptoms of nervous system involvement; 21 had some significant abnormality of the nervous system which was apparently related to anemia. However, neurologic sequellae were noted in eight patients who never were anemic. Sixteen patients had evidence of tetany; eight patients had combination of both nervous system involvement and tetany. Four patients are reported in detail, three of whom had marked involvement of the nervous system, primarily a myeloradicu-

loneuropathy. Since one of the latter had had syphilis, only two of 94 patients had severe manifestations of nervous system disease which could be reasonably attributed wholly to the malabsorption syndrome.

There were sixteen patients who only suffered from tetany and twenty-two other patients with signs of neurologic involvement such as paresthesias, absent reflexes, sensory abnormalities, without tetany. The reason for this mutual exclusion is not clear.

The therapeutic management of patients suffering from the malabsorption syndrome with neurologic manifestations is discussed.

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OSSEOUS CHANGES AND FRACTURES IN THE MALABSORPTION SYNDROME

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The insidious development of bone pains and/or fractures without trauma in patients who have inadequate intestinal absorption because of sprue has brought to our attention the problem of bone changes and orthopedic management of these patients. The changes have been known and reported in the literature (1-14) but deserve emphasis.

It has been established that patients suffering from idiopathic steatorrhea, and other causes of malabsorption, suffer defects in proper absorption of fats, particularly the saturated fats. Associated difficulty in absorption of the fat-soluble vitamins causes hypovitaminosis D and has a deleterious effect on maintenance of proper mineralization of the bones. Malabsorption of vitamin D prevents proper absorption of calcium (15) and causes osteomalacia, mild degrees of which are commonly seen in patients with the malabsorption syndrome (Figs. 1 and 2). Roentgenograms for intestinal studies frequently disclose asymptomatic osteomalacia of the spine as an incidental finding. In cases other than sprue inadequate intake of vitamin D or its faulty utilization will produce the same clinical picture. Patients with "incomplete sprue" may manifest little or no diarrhea and yet develop osteomalacia (16, 17).

The distinction between osteomalacia and osteoporosis must be kept clearly in mind (18, 19). Osteomalacia in general, whether associated with sprue or not, is an adult form of rickets resulting from a lack of vitamin D and sunshine. This in turn prevents proper absorption of calcium and impairs calcium salt deposition in the bone matrix (osteoid). Both the serum calcium and serum phosphorus concentrations may be normal or low, while the blood alkaline phosphatase concentration is usually elevated. In regions where proper diet and exposure to sunshine exists, osteomalacia from deficiencies of these two factors is quite infrequent. However, in these regions osteomalacia may be seen as a secondary effect in conditions where there is malabsorption of the fat-soluble vitamin D in the intestinal tract and/or a lack of adequate food intake (20).

Osteoporosis, on the other hand, is a state of deossification, an actual thinning of bone trabeculae due to a defect in protein matrix. It is a disease of tissue metabolism and not of calcium metabolism. Adequate ingestion, absorption and transportation of vitamin D and minerals may be present but osteoporosis, nevertheless will exist. Serum calcium, phosphorus and alkaline phosphatase levels are relatively normal (18). It is seen mostly in post-menopausal, disuse, post-traumatic and senile states and in Cushing's syndrome. It occurs less commonly in other conditions such as scurvy and acromegaly, or it may be

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FIG. 1. Incidental finding of osteomalacia in a case of sprue without skeletal symptoms. Forearm bones shown.

idiopathic. Osteoporosis produces roentgenologic changes in the vertebrae and pelvis, and less frequently in the skull and the extremities.

Progressive softening of the bone from osteomalacia alone or osteomalacia plus osteoporosis results in a weakened skeletal supporting structure which may not sustain the mechanical requirements of ordinary living. An interruption or collapse of osseous structure may develop without external trauma. So-called pseudo-fractures of the pubis are most common. Next in frequency are lesions of the femoral neck, axillary border of the scapula, and ribs (21).

CASE REPORTS

Three instances of slowly developing osteomalacia in known cases of primary sprue were encountered in which osseous discontinuity occurred. A fourth instance appeared in a patient who had a subtotal gastrectomy two years previously.

Case 1

P. S., a 57-year old, white, Jewish salesman, gave a history of diarrhea in World War I, but his first symptoms of sprue appeared in 1931. In 1948 the diagnosis of sprue was definitely established on the basis of laboratory tests at The Mount Sinai Hospital, but it is reasonable to suppose that the diarrhea in World War I represented idiopathic steatorrhea.



FIG. 2. Humerus of same case as in Fig. 1

Because of an unsatisfactory response to therapy, he was treated with 80 mg. of hydrocortisone daily, which was effective in relieving his symptoms of sprue. Later, the dose was reduced to 40 mg. daily and maintained at that level. After 18 months of cortico-steroid therapy he was readmitted to the hospital (April 5, 1955) because of pain and weakness of his left lower extremity.

The positive physical findings consisted of a limp due to pain and weakness of the left lower extremity, and a shuffling gait. Neurologic examination disclosed diminished biceps reflexes bilaterally, absent left cremasteric reflex and diminished vibratory sensation of feet and the fourth and fifth fingers of the hands. Motions of the left hip were limited and painful. Mild diffuse spinal tenderness was present. Serum calcium and phosphorus values were both low and the blood alkaline phosphatase was elevated. The lowest serum calcium concentration was 7.8 mg. per cent and the lowest serum phosphorus concentration was 1.3 mg. per cent. The highest blood alkaline phosphatase was 11 King-Armstrong units. During therapy the serum calcium and phosphorus concentrations returned to normal. The blood alkaline phosphatase was then 10 King-Armstrong units.

X-ray studies revealed generalized deossification of the bones, fish-shaped intervertebral spaces, a pseudo-fracture through the neck of the left femur (Fig. 3), early degenerative changes of both hips, transitional fifth lumbar vertebra, slight compression of the body of L₄ and an old healed fracture of the right clavicle.

Internal fixation was performed by means of a Lippmann corkscrew bolt (Fig. 4). The patient's post-operative course was characterized by dramatic improvement of his left lower

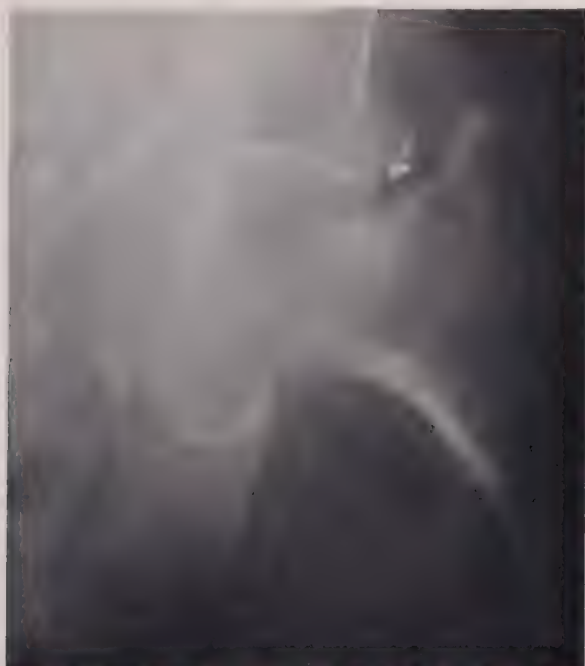


FIG. 3. Case 1, osseous discontinuity in neck of left femur in a case of malabsorption syndrome (sprue) treated with cortico-steroid.



FIG. 4. Case 1, after internal fixation with Lippmann corkscrew bolt.

extremity pain. His gait became painless and normal appearing. Androgen-estrogen therapy, high protein diet, vitamins and calcium were administered. Two years after the operation the patient was still doing well. He was still on small doses of corticosteroids and was in remission as regards his sprue.

Comment: A patient with sprue of long duration treated with corticosteroids is presented. Studies disclosed severe osteomalacia and superimposed osteoporosis which resulted in a fissure fracture of the neck of the femur and a compression fracture of the fourth lumbar vertebra. Internal fixation of the fracture was performed with excellent result.

Case 2

C. L., a 62-year old, Puerto Rican female, was a known case of primary malabsorption syndrome (idiopathic sprue) associated with a macrocytic anemia (August 1955). She improved under treatment at The Mount Sinai Hospital with folic acid and vitamin B₁₂. The macrocytic anemia improved and microcytic anemia appeared, but there was no change in the diarrhea. This remained refractory to treatment until prednisone was added to her regimen. Lowest values of serum calcium and phosphorus concentrations were 9.4 mg. per cent and 2.8 mg. per cent, respectively. The blood alkaline phosphatase level was 22 King-Armstrong units. After clinical improvement was manifest, the values of serum calcium and phosphorus became normal. Her blood alkaline phosphatase level was then 8.8 King-Armstrong units.

On February 28, 1956, seven months after corticosteroid treatment was started, she fell and developed pain in the left hip. X-rays revealed generalized deossification, a valgus type



FIG. 5. Case 2, complete fracture, neck of femur in a case of malabsorption syndrome (sprue) with osteomalacia.



FIG. 6. Case 2, compression of body of twelfth dorsal vertebra.



FIG. 7. Case 2, after internal fixation with Lippmann corkscrew bolt.

fracture of the neck of the left femur (Fig. 5) and compression of the body of the twelfth dorsal vertebra (Fig. 6). Internal fixation by means of a Lippmann corkscrew bolt was performed (Figs. 7 and 8). Her post-operative course was uneventful. Ambulation was started promptly, weight bearing initiated three weeks later and the pain in her hip disappeared. However, pain in the back persisted. Continued small doses of prednisone were required for relief of her sprue symptoms.

Comment: A patient with idiopathic sprue who was refractory to usual treatment, but relieved by prednisone, is presented. Severe osteomalacia and osteo-

porosis resulted in fracture of the neck of the left femur and a compression fracture of the twelfth dorsal vertebra. Internal fixation of the hip fracture was performed with improvement.

Case 3

N. F., a 43-year old, white male, was born in Italy and came to New York City at the age of 19. He was well until 1942, when he developed severe, watery, non-bloody diarrhea, with foul smelling stools, vomiting, weakness, anorexia and weight loss. Since that time, he has had intermittent attacks with exacerbation and remissions. In 1948, he suffered a fracture of the left hip and was treated at another hospital. He was admitted to other hospitals a number of times before coming to The Mount Sinai Hospital on December 8, 1953. His first ex-



FIG. 8. Case 2, lateral view.

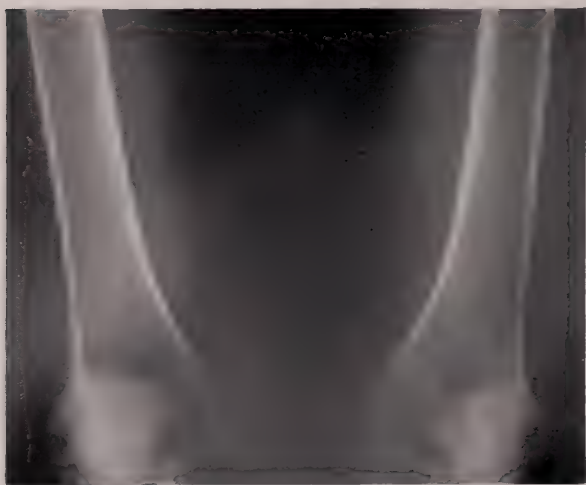


FIG. 9. Case 3, Osteomalacia of femora, malabsorption syndrome (sprue) of long standing.



FIG. 10. Case 3, Osteomalacia of forearm bones.

amination at The Mount Sinai Hospital revealed him to be an emaciated, chronically ill, white male of very short stature with marked kyphoscoliosis who was unable to walk unassisted. Neurologic changes indicative of posterior column disease were present. Detailed studies indicated the presence of non-tropical sprue with hyperchromic anemia. Blood chemical studies revealed the lowest value of serum calcium to be 5.9 mg. per cent, serum phosphorus 2.7 mg. per cent. The highest value of blood alkaline phosphatase was 24 King-Armstrong units. For over one year prior to admission he received injections of ACTH. A roentgenologic bone survey revealed a marked degree of generalized demineralization (Figs. 9 and 10). The vertebrae had a biconcave appearance (Fig. 11). There were old healed fractures of the right scapula and right clavicle (Fig. 12). There was also a healed fracture of the left hip. He improved under medical treatment consisting of vitamin B₁₂, intravenous iron and 80 mg. of hydrocortisone daily. Blood serum calcium increased to 8.6 mg. per cent; serum phosphorus to 4.5 mg. per cent. Blood alkaline phosphatase decreased to 18 King-Armstrong units. Sulkowich test of urine was negative. He was discharged on September 9, 1954, ten months after admission, very much improved and was continued on 40 mg. of hydrocortisone daily. However, his neurologic status did not change. He was then transferred to a convalescent institution.

On November 13, 1956, he was re-admitted to The Mount Sinai Hospital because of increasing numbness of the hands and feet. Examination revealed posterior column disease and peripheral nerve involvement. The anemia which originally was of the hyperchromic

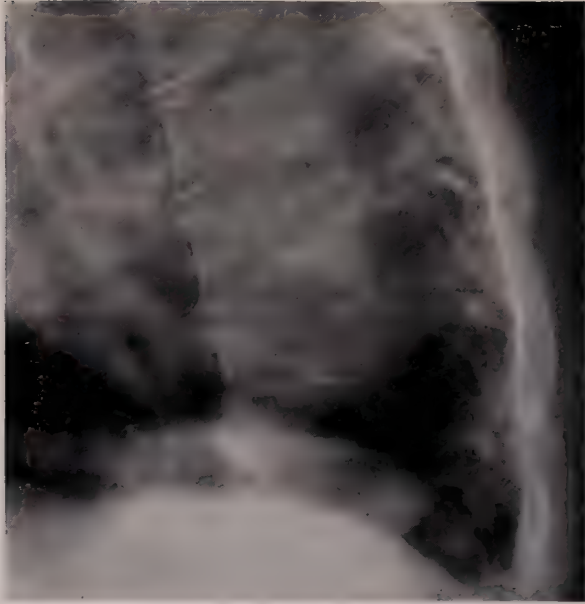


FIG. 11. Case 3, compression of bodies of dorsal vertebrae, Osteomalacia (outlines of bodies touched up).

type was now hypochromic. Roentgenologic skeletal survey revealed persistence of marked generalized demineralization, including the bioconcave appearance of the vertebra and the previously noted healed fractures. Although there was no worsening of the demineralization and no new fractures, there was no distinct improvement in the status of his skeletal system.

Comment: The patient was a 43-year old male with long standing sprue who developed osteomalacia and a number of fractures at different times in different regions. Injections of ACTH resulted in improvement. Persistent anemia and posterior column disease over-shadowed his bone problem.

Case 4

W. S., a 63-year old, white male, presented himself with a complaint of pain in the right lower extremity of six months duration. For 20 years he suffered from a gastric ulcer. Two years prior to his present complaint, he underwent a successful gastric resection. The pain in his right hip was slow in onset and radiated distally into the lower extremity. He had been treated by other physicians for lumbrosacral strain and sciatica without improvement.

On examination there was definite pain and limitation of motion in the right hip. Internal rotation and abduction were limited and painful. The circumference of the right thigh measured one inch less than the left. Neurologic examination was negative. A roentgenogram of the hip revealed osteomalacia and a definite fissure fracture of the neck of the right femur without displacement (Fig. 13). Internal fixation with a Smith-Petersen nail was performed at a private hospital with prompt relief of his pain (Fig. 14). Weight bearing was permitted in five days. His post-operative course was uneventful. Unfortunately, he was not studied as a malabsorption problem but it was considered that he was a case of osteomalacia secondary to post-gastrectomy sprue.



FIG. 12. Case 3. indenting of lower ribs and healed fracture of right clavicle.

Comment: Two years after gastrectomy for long standing ulcer, this patient suffered a fracture of the neck of the femur associated with osteomalacia, probably secondary to malabsorption steatorrhoea. Internal fixation was performed with excellent result.

MECHANISM OF THE DEVELOPMENT OF BONE CHANGES IN MALABSORPTION SYNDROME

The metabolism of the osseous structures of adults is highly dynamic and continuously undergoing steady concomitant break-down and build-up of bone. Organic bone matrix (osteoid) is the basic framework. Mineralization of this lattice work completes the formation of bone.

In sprue and other malabsorption syndromes the intestine fails to absorb fats properly. This results in failure to absorb fat-soluble vitamins, especially vitamin D, which in turn prevents absorption of calcium (15). In addition to the malab-



FIG. 13. Case 4, 18 months after subtotal gastrectomy for ulcer of 20 years duration, osseous discontinuity in neck of femur associated with pain and osteomalacia.



FIG. 14. Case 4, after insertion of Smith-Petersen nail. (Note that post-operatively the osseous discontinuity was more apparent across the entire neck of the femur).

sorption of calcium caused by vitamin D deficiency, considerable amounts of calcium remain unabsorbed because of a combination with the excessive fatty acids in the bowel and the formation of insoluble soaps (17). It is well known that disturbances of pancreatic function as well as disturbances of biliary function impair fat absorption. Ileostomies, extensive resection of the bowel and diffuse intestinal disease may prevent absorption of properly digested fats and vitamins.

Whatever the reason for the deficiency, loss of calcium from the body initiates compensatory mechanisms to restore proper balance (Table I). An increased secretion of parathormone causes breakdown of organic bone matrix, thus releasing bone minerals and restoring blood calcium levels (23). But parathormone also diminishes phosphate reabsorption of the kidney tubules and brings about increased phosphaturia. Loss of phosphate evokes an increase of calcium in the blood from the osseous reservoir (24, 25). A vicious circular process is thus initiated requiring more parathormone to free more calcium to the interstitial tissues and at the same time producing increased excretion of phosphate. As this process continues the osseous structures suffer significant loss of minerals. The feces demonstrate increased fat and calcium content. A diminished urinary calcium excretion develops. When loss of available minerals continues, osteomalacia develops. However, the degree of osteomalacia in sprue bears some

TABLE I.
Schematic presentation of development of osteomalacia

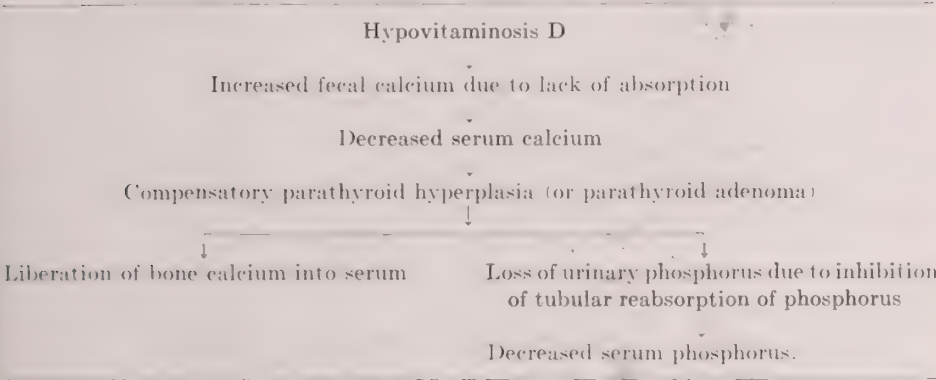


TABLE II
Chart showing highest and lowest values of serum calcium, phosphorus and alkaline phosphatase

CASE	AGE	SERUM		
		Calcium mg. 100 ml.	Inorganic Phosphorus mg. 100 ml.	Alkaline Phosphatase, King-Armstrong units
1	57	Lowest 7.8	Lowest 1.3	Highest 11
		Highest 10.1	Highest 4.0	Lowest 10
2	62	Lowest 9.4	Lowest 2.8	Highest 22.0
		Highest 10.4	Highest 3.7	Lowest 8.8
3	43	Lowest 5.9	Lowest 2.7	Highest 8.6
		Highest 8.6	Highest 4.5	Lowest 4.6

relation to the degree of exposure to sunshine (26). Excellent observers in the tropics have not seen osteomalacia complicating sprue. The more exposure to sunshine the less the osteomalacia.

A large amount of mineral loss, perhaps as much as 50 per cent, must develop before roentgenographic changes become apparent. This accounts for instances where the blood changes of osteomalacia are present, but the roentgenograms do not reveal demineralization. Fissures in the cortices of the long bones appear. These represent uncalcified osteoid tissue (16, 27). They are variously described as pseudo-fractures, Looser zones or "Umbauzonen" (2). Multiple spontaneous symmetrical pseudo-fractures are referred to as Milkman's syndrome and are manifestations of the same underlying process (3). It has been suggested that the narrow bands of diminished density, which often appear symmetrically and last for months to years in the skeletons of patients with osteomalacia, correspond to the location of main blood vessels which lie on the bones. The mechanical stress caused by the vessels could cause small breaks in the cortex with subsequent laying down of callous, which, in osteomalacia, is uncalcified. This proposed mechanism could explain the symmetrical appearance of the pseudo-fractures in otherwise normal appearing bones and their location at sites not usually subjected to other mechanical stresses (21). If the bone is weakened sufficiently, fractures may result from minor trauma. True pathologic fractures without external trauma may also develop.

In patients with post-gastrectomy sprue the exact mechanism of the defect of absorption has not been studied. It is likely that the existing steatorrhoea is an important factor.

The Role of the Parathyroids

The response of the parathyroid glands to the lowering of serum calcium in sprue may be one of compensatory increase of activity or one of what might be termed parathyroid insufficiency. When hyperparathyroidism occurs in response to the lowered serum calcium, the stimulus to osseous release of calcium deposits aids in maintaining adequate levels of serum calcium. At the same time serum phosphorus is lowered, owing to loss of urinary phosphates. The serum calcium and phosphorus levels are both low. In a long-standing case of sprue in a 41-year old female recently reported, it was noted that the serum calcium was above normal and serum phosphorus low (28). Roentgenograms revealed that a previously noted osteomalacia had progressed into an osteitis fibrosa generalisata. She improved after two parathyroid adenomas were removed. The authors concluded that as a result of her lifelong steatorrhoea she probably passed through a phase of parathyroid hyperplasia before the two adenomas developed. Thus, they concluded, although compensatory hyperparathyroidism is usually reversible following administration of vitamin D, in some cases of long standing steatorrhoea this will not obtain. One or more parathyroid adenomas may develop which will require surgical removal. Despite these findings, one may still raise the question of why some sprue cases develop osteomalacia and some do not? According to some authors (6) it appears to depend on the degree of second-

ary hyperparathyroidism. If parathyroid insufficiency is present calcium is not mobilized from the bones, serum calcium remains low and tetany may develop. It therefore appears from present evidence that the response of the parathyroid in sprue with either increased function or insufficiency is a secondary factor and not primary. In the absence of techniques for the quantitative determination of circulating parathormone in the blood, the exact role of the parathyroids remains unclear.

DISCUSSION

The proper evaluation of symptoms in idiopathic sprue may require some analysis. Aside from the diarrhea, which may or may not be present, the development of anemia, posterior column and peripheral nerve involvement, and bone softening may cause intermingling and overlapping symptoms. In occult, latent or incomplete sprue, diarrhea is not a prominent feature. Obscure cases of osteomalacia could thus be properly explained (17). The clinician may encounter paresthesias, irritability, tetany and regional pains. In analyzing the cause of pain the clinical picture may suggest arthritis, neuritis, fibrositis or herniation of the nucleus pulposus. Neurologic involvement may appear to be the obvious cause when underlying bone changes are the real instigator of muscular atrophy and weakness. Bone pain may be associated with a developing osteomalacia even in the absence of pseudo-fractures (3). Progressive softening of the bone resulting from osteomalacia may be aggravated by a superimposed osteoporosis—post-menopausal, senile or secondary to corticosteroid therapy. The weakened skeletal structure may become susceptible to lesser degrees of external trauma or even unable to withstand the mechanical requirements of ordinary living. In either situation an interruption or collapse of osseous structure may develop. One of our patients (case 1) was admitted to the neurological service for a sciatic syndrome with atrophy of the left thigh. On x-ray examination of the bones, a fissure fracture of the neck of the femur was discovered as the true cause of his pain. Following internal fixation he improved rapidly, was free of pain and able to ambulate well within a few days.

Differential diagnosis between osteomalacia and osteoporosis is possible in many instances. Roentgenograms in osteomalacia disclose a generalized demineralization, whereas in osteoporosis it is manifested mostly in the spine and pelvis. Serum calcium, phosphorus and alkaline phosphatase are normal in osteoporosis but are altered in osteomalacia. The Sulkowich test is positive in osteoporosis and negative in osteomalacia. Despite the differential features listed above many patients will present intermingling of osteomalacia and osteoporosis and simultaneous treatment of both conditions is indicated.

ORTHOPEDIC MANAGEMENT

The treatment of fractures in sprue or malabsorption in addition to general therapy consists of reduction and or fixation. Internal fixation for fractures of the neck of the femur, and the use of braces and early ambulation for compression fractures of the spine are employed. Present day trends in orthopedics have

drifted away from the older idea of attempting hyperextension reduction of compression fractures of the spine and the application of a full body cast. Instead, a brief period of rest sufficient to alleviate the pain is favored, followed as soon as possible by gradual increasing ambulation with the support of a back brace (29).

Decreased physical activity tends to increase deossification. Correction of the underlying malabsorption is essential. However, as illustrated in some of our cases, failure to respond to the treatment of sprue may necessitate the use of corticosteroids. Since this form of therapy, although beneficial to idiopathic steatorrhoea, will aggravate the bone softening and add osteoporosis to the osteomalacia, corticosteroids must be held in reserve and employed only when all other methods have proved inadequate. It is claimed that prednisone and prednisolone have less of a deossifying effect than other corticosteroids but further observations are necessary before this is confirmed in cases of malabsorption syndrome. The smallest effective dose should be used and osteoporosis must be counteracted by high mineral and high protein intake. Vitamin D should be employed, preferably parenterally. Ultraviolet radiation to the skin would also be helpful. In some instances as much as 300,000 units of vitamin D should be administered daily (8). Testosterone should be used in suitable doses.

CONCLUSIONS

1. Observations on the occurrence of osteomalacia, usually associated with osteoporosis, in the malabsorption syndrome are reported.
2. Three cases in which idiopathic sprue was the underlying cause of the osteomalacia and one case in which bone changes followed a subtotal gastrectomy (post-gastrectomy sprue) are presented.
3. The mechanism of development of osteomalacia and osteoporosis is reviewed and the role of the parathyroid is discussed.
4. Corticosteroids, although helpful in the control of idiopathic steatorrhoea, enhance osteoporosis and further embarrass osseous integrity.
5. Management of the underlying osteomalacia and osteoporosis and treatment of the fractures is discussed.
6. Incomplete sprue may cause osteomalacia despite the absence of overt intestinal symptoms.

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THE ROENTGEN FINDINGS IN THE MALABSORPTION SYNDROME

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It has been known for many years that disorders of absorption from the gastrointestinal tract may be reflected in abnormalities of the radiographic pattern of the small intestine. The essential features of this pattern are dilatation, segmentation, hypersecretion, changes in motility and mucosal markings. These changes have been considered non-specific since they occur in a variety of conditions, some associated with diseases of malabsorption, such as sprue, Whipple's disease, and lymphosarcoma, but also in many other conditions having no relation to malabsorption, such as hookworm disease, hyperthyroidism, allergy and emotional disturbances. Numerous terms have been used loosely to bind the roentgen findings in these heterogeneous conditions, i.e. deficiency pattern, disordered motor function, segmentation or irritation patterns and enteropathy in deficiency states (1). Minimal degrees of dilatation, segmentation and hypersecretion may occur in many unrelated diseases. When the changes are marked and occur in particular combinations, however, they are usually found only in association with certain malabsorptive states, namely, sprue, lymphosarcoma and Whipple's disease. The roentgen findings, therefore, are more specific than hitherto suspected and sufficiently characteristic to be of diagnostic value.

The term malabsorption syndrome has recently been applied to diseases which are characterized by alterations in absorption of nutrients from the intestinal tract. Fats, because of their insolubility in aqueous solutions, are relatively difficult to absorb. It follows, therefore, that difficulties which patients have with intestinal absorption, are often characterized by excessive amounts of fat in the stool, i.e. steatorrhea.

The causes of symptomatic steatorrhea can be classified into three main groupings:

1. Idiopathic steatorrhea
2. Pancreatogenous steatorrhea
3. Secondary steatorrhea (organic lesions of the gastrointestinal tract).

Since these three groups represent the majority of the cases with symptomatic steatorrhea, the roentgen findings encountered in these cases will be described.

HISTORY

The first recorded roentgen studies of the intestinal tract in patients with sprue were reported by Pillai and Murthi in 1931. They studied nine cases of

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sprue in India and noted changes in motility and tone of the stomach and colon. The small intestine emptied rapidly and in one case "a part of the terminal coil of the ileum was dilated. The cecum showed dilatation . . ." (2). In 1932, Bennett, Hunter and Vaughan, reporting 16 cases of idiopathic steatorrhea, noted the roentgen changes in the intestinal tract were largely confined to the colon, which manifested slight to extreme dilatation. They commented that the abdominal distention which is such a conspicuous feature of this disease also could be due to the small intestine (3). Mackie, in 1933, reported a case of non-tropical sprue which showed dilated coils of jejunum suggesting a lack of tone. Hypermotility was also noted (4). Snell and Camp, in 1934, in a report of seven cases of chronic idiopathic steatorrhea, were the first to report in detail the roentgen alterations in the small intestine. They observed delayed motility, changes in mucosal relief occasioned by smoothing of the bowel contours, and obliteration of the valvular markings. The barium was observed to clump in elongated masses. They stated that these findings were not characteristic of this disorder, but "may occur in varying degrees in any diffuse inflammatory condition of the intestinal tract" (5). Mackie, Miller and Rhoads (1935) reported on the roentgen changes in the small intestine in 17 cases of sprue. These authors appear to be the first to have utilized the term "segmentation" to describe the segmental distribution of barium within the small intestinal loops. In addition to the findings previously reported by Snell and Camp, they noted dilatation of the bowel lumen (6). Following these reports, similar small intestinal changes were noted in many varied conditions, chronic ulcerative colitis (7), chronic idiopathic adult tetany (8), celiac disease (1), pancreatic insufficiency (9), icterus (10), lymphosarcoma (11), allergy (12, 13), Whipple's disease (14) and tuberculosis (15).

To the growing roentgen literature on sprue, Kantor (1939) contributed the term "moulage" to describe the appearance of the bowel in this condition which "resembles a tube into which wax has been poured and allowed to harden" (16).

In 1941, Golden, correlating previous reports with observations on his own cases, noted the similarity in the roentgen appearance of the small bowel in a multitude of clinical entities as well as that seen in normal newborns. He postulated a common mechanism operating in the production of these similar phenomena from so many causes, i.e. damage to the intramural nervous system of the small intestine. To describe these roentgen findings, he introduced the term "deficiency pattern" because so many of his early cases were actually deficiency states (17, 1). It soon became apparent that the cases were not necessarily associated with deficiency diseases and the terms "disordered motor function" or "irritation pattern" were preferred. Despite the confusing nomenclature, these terms served to focus attention upon these little-known and elusive small intestinal disorders.

Sussman and Wachtell (1942, 1943) did not concur in the hypothesis that there was a common neurogenic mechanism operating in producing this pattern. By giving atropine to tolerance to normal subjects, the "deficiency pattern" could not be produced. They concluded, therefore, that degeneration of the intramural nerve plexuses was not a factor. Based on the postulate that the

pattern in sprue might be caused by overactivity of the parasympathetic nervous system, large doses of atropine were given to sprue patients without significantly altering the roentgen findings. Concluding that the findings of the "deficiency pattern" are not necessarily variations of a single pattern with a common neurogenic cause, they stated that submucosal changes, muscle or nerve damage, modified by abnormal bowel content or unusual hormonal or nervous stimuli, could individually or in combination produce this pattern (18, 19).

Utilizing balloon techniques in two patients with sprue, Ingelfinger and Moss (1943) demonstrated that the small intestine in sprue lacks tone, possibly accounting for the ineffectiveness in advancing intestinal contents and thus producing segmentation. Furthermore, they observed that intestinal contractions responded to Mecholyl and not to Prostigmin and suggested that the nervous apparatus of the small intestine in sprue fails to liberate active acetylcholine (20).

Attempts have been made to reproduce in normal subjects the small bowel pattern in sprue. In 1936, Pendergrass, Ravdin, Johnston and Hodes studied the effects of various foodstuffs on the small intestinal pattern. With an olive oil-barium-water preparation they were able to produce a picture similar to that seen in some cases of sprue, with minimal segmentation, hypomotility and some dilatation of the bowel lumen (21). In 1949, Frazer, French and Thompson were able to induce segmentation and produce a picture which they considered to be radiologically indistinguishable from the "deficiency pattern" by the introduction of fatty acids, hypertonic solution or mucus into the small intestine of a normal individual. They produced flocculation of barium *in vitro* when added to mucus-containing secretions and attributed the segmentation pattern in sprue to increased mucus content of the bowel produced by the irritation of fatty acids. It was suggested by these investigators that, unless the possibility of flocculation of barium has been excluded, the segmentation pattern cannot be regarded as evidence of vitamin deficiency or disordered motor function (22). Ardran, French and Mucklow (1950), utilizing a non-flocculating barium suspension in patients who had previously shown a segmentation pattern with routine barium preparations, were able to prevent segmentation and maintained the contrast agent in a continuous column, noting only dilatation (23). It has become apparent, therefore, that the segmented clumps of barium do not reflect the morbid anatomy of the surrounding intestine because they do not outline the bowel wall and interpretation of mucosal alterations or narrowing of the lumen under these circumstances may be misleading.

In 1954, Adlersberg et al. and Marshak, Wolf and Adlersberg, describing the clinical and roentgen alterations they observed in 40 patients with idiopathic sprue, presented the concept of the sprue pattern. This pattern consisted primarily of dilatation of the small intestinal loops, hypersecretion and segmentation. They considered that when this pattern was observed with sufficient intensity, the diagnosis of sprue could be suggested radiologically (24, 26).

TECHNIQUE OF ROENTGEN STUDY

The small intestine was studied following the administration of a mixture containing 10 ounces of barium sulfate by volume to which had been added enough water to make 20

fluid ounces. The ordinary commercial USP barium sulfate preparation was used. The initial film was made at 15 minutes and another after a 15 minute interval. Further filming depended on the rate of passage of the barium meal and usually consisted of an examination every 30 to 60 minutes until the barium left the small intestine. It was occasionally necessary when large segments of small intestine pooled the barium to administer an additional four or six ounces of the mixture to secure adequate visualization of the small intestine. Neither saline nor icewater were administered because these preparations in themselves, in our experience, disturbed the small intestinal pattern.

In the interpretation of diffuse lesions of the small intestine, large quantities of barium should be used so that many intestinal loops may be visualized in continuity at the same time. In sprue, for example, the loops of bowel may be so dilated that small amounts of barium administered may pool in a single segment. Small amounts of barium may not reflect the morbid anatomy of the small intestine due to incomplete filling and frequently the incomplete distention may simulate an abnormality.

Ardran, French and Mucklow have stated that with the use of their micropulverized barium preparation, segmentation which is so frequently seen in malabsorptive states can be prevented and a continuous barium column produced (23). This is advantageous in recognizing the organic structure of the small intestine. It may have the disadvantage, however, if used on the initial examination, of obscuring the functional changes which may aid in the diagnosis of malabsorptive states.

THE ROENTGEN FINDINGS IN IDIOPATHIC STEATORRHEA OR SPRUE

Forty-six patients with sprue were studied. Some of these findings have been previously reported (24, 26). In six patients, a normal small intestinal pattern was found. The remaining 40 patients exhibited in varying degrees the small intestinal changes that have been described by many authors, namely, dilatation, segmentation, fragmentation and scattering of the barium column, thickening of the mucosal folds, hypersecretion, fluid levels, the "moulage sign" and motility changes (24, 25, 17, 1, 26).

Dilatation. Dilatation of the lumen of the small intestine is one of the most important and constant findings in sprue. Some of the individual features of the sprue pattern are seen in other disorders, but in none is dilatation more striking or constant than that associated with sprue.

Dilatation is the most frequent of the roentgen findings in sprue and was found in 40 of 46 cases. It is usually best visualized in mid- and distal jejunum (Figs. 1A and 1B). Dilatation of the distal ileum is not as common as elsewhere in the small intestine. In three cases, the entire small intestine was dilated. The dilated loops are generally long and tortuous in course with pliable walls. The *valvulae conniventes* are prominent (Figs. 2A and 2B). The degree of dilatation is exceedingly variable and often a single intestinal segment may manifest varying degrees of dilatation during the course of a single roentgen study. In four cases, dilatation was marked (Fig. 3A). In 16 cases, the lumen of the dilated intestinal loops was three times the normal caliber; in 16 patients the dilatation was twice normal and in four patients, it was mild. In general, however, dilatation appears to be related to the severity of the disease and was most marked in the advanced cases. The large intestine may also show dilatation which can be pronounced.

Fluoroscopic observations of the altered contractility of the dilated small intestinal loops are of some interest. In many patients, the barium column flowed more freely than usual through the dilated intestinal loops, apparently

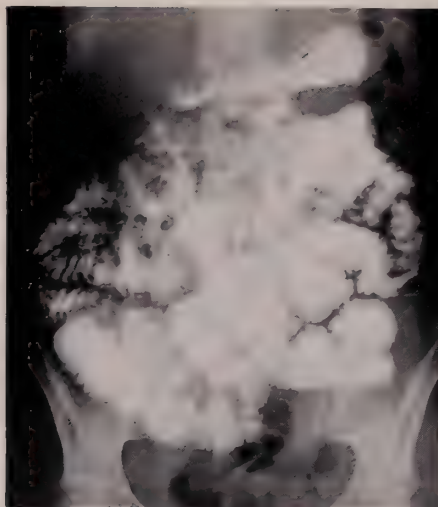


FIG. A

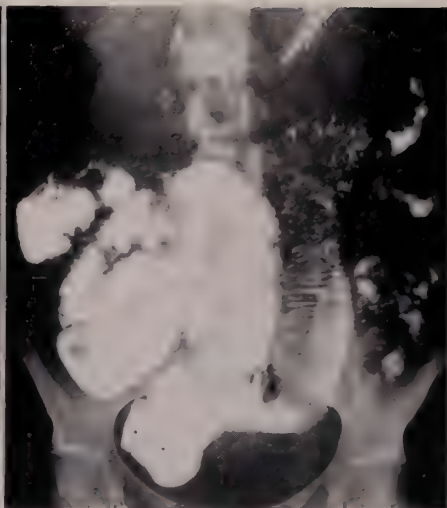


FIG. B

FIG. 1A. Moderate dilatation of mid- and distal jejunum.

FIG. 1B. Moderate dilatation of mid- and distal jejunum. Note the "functional intussusception" at the end of the barium column.



FIG. A



FIG. B

FIG. 2A. Moderate diffuse dilatation of the jejunum with prominent valvulae conniventes.

FIG. 2B. Moderate dilatation of the mid-jejunal loops with prominent valvulae conniventes. The loops are pliable.

unhindered by the tone of the contracted segment found normally ahead of the barium column. When secretions were encountered, progress was slowed and the column segmented. Conversely, in some patients with marked dilatation, there was prolonged transit time which appeared to be due to ineffective peristaltic activity. These fluoroscopic findings suggest that the tonicity of the small intestine in sprue is altered, offering little resistance to dilatation by ingested substances, possibly even secretions, and that, once dilated, peristalsis becomes



FIG. A



FIG. B

FIG. 3A. Marked dilatation of mid- and distal jejunum with prominence of mucosal folds. At autopsy, the mucosa of the small intestine was flat and atrophic.

FIG. 3B. Delayed segmentation. The intestinal loops are dilated. Secretions are increased and there is fragmentation of the barium column.

disordered and ineffective. It has been shown experimentally that, if the intraluminal pressure within an isolated loop of small intestine is increased beyond a certain point, the stretch reflex is no longer in operation and the bowel wall will not contract (27). Decompensation of the bowel wall may occur in severe cases of sprue with marked prolonged small intestinal dilatation.

Secretions, in themselves, do not appear to be a factor in the production of dilatation. Dilatation is generally most marked in the jejunum where secretions are least, and minimal in the ileum, where excessive secretions are most often found.

Patients with prolonged diarrhea due to any cause may develop potassium deficiency. In animals, dilatation of the small intestine has been produced following potassium depletion. It appears that potassium is necessary in the mediation of nerve impulses and the alterations in potassium may produce an autonomic imbalance (1). If this is a factor, why only the small intestine is affected, and not other autonomic functions such as sweating or pilomotor activity, is of considerable interest.

The cause of dilatation remains unknown. At autopsy, the only finding may be thinning of the small intestinal wall. Whether this finding is the cause of the dilatation or its sequela has been subject to speculation.

Segmentation. Segmentation was seen in 32 of 40 patients with abnormal small intestinal patterns. The term segmentation in this study has been restricted to indicate only those masses of barium which are large, definitely separated from adjacent clumps, usually dilated and contain excessive secretions. The small, contracted, barium-filled segments of small intestine connected by strands of barium seen in association with spasm are not included in this definition.

Segmentation was most pronounced in the ileum and was best seen in the more advanced cases. Two forms were noted, immediate and delayed. The more common form was delayed segmentation, i.e. segmentation that occurred in those intestinal segments that were in the process of evacuation (Figs. 3A and 3B). The less common, immediate segmentation was noted as soon as the barium entered the small intestine and persisted throughout the study (Figs. 4A and 4B). In a mild or moderately severe case of sprue, diffuse dilatation of the jejunum and proximal ileum was noted followed by segmentation of the barium column in the distal ileum (delayed) (Figs. 7A and 7B). In the more severe cases, segmentation was immediate (Fig. 4A). The difference between the two forms of segmentation may be accounted for by the amount of secretions within the intestinal tract. In those patients with markedly increased secretions, segmentation appeared to be immediate.

Between the segmented clumps of barium, worm- or string-like strands of barium were often noted. These seemingly collapsed intestinal loops were usually associated with segmentation. They were inconstant and varied from film to film appearing to be due to possibly altered motor activity of the bowel segment or to incomplete filling and emptying (Figs. 5A and 5B). Since these seemingly collapsed segments only occurred in the presence of segmentation (which was always associated with hypersecretion), they may actually represent only the barium stream as it passes through a secretion-filled loop (Figs. 5A and 5B).

As the barium leaves the small intestine, a faint, irregular stippling of residual barium may be seen along the course of the jejunum. This is a normal finding. However in sprue, the mottling is coarser and more amorphous, resembling soap flakes. This is called scattering and is usually associated with segmentation and increased secretion. The term fragmentation has also been used to describe this finding (Figs. 3B and 4B).

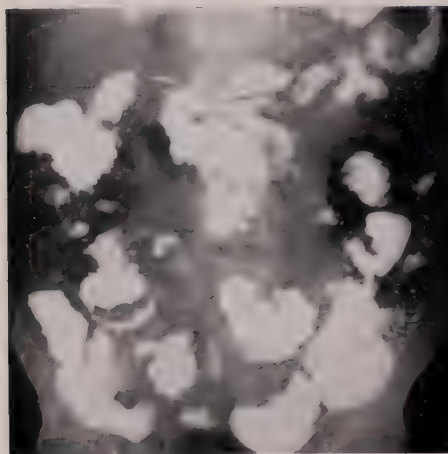


FIG. 4A

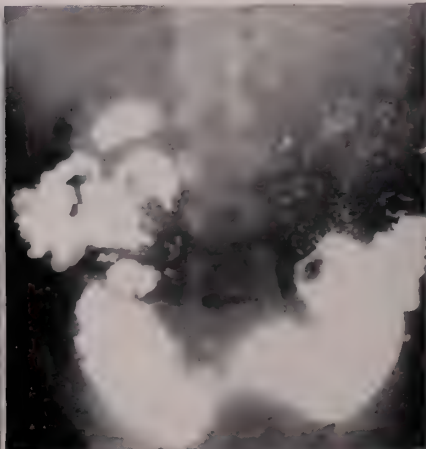


FIG. 4B

FIG. 4A. Immediate segmentation occurring throughout the small intestine.

FIG. 4B. Immediate segmentation with moderate dilatation. There is fragmentation of the barium column in the jejunum.

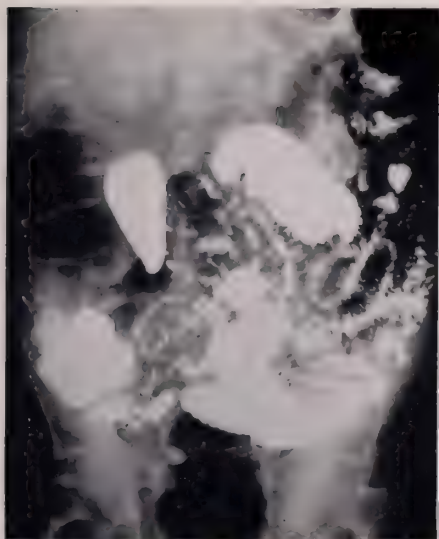


FIG. 5A



FIG. 5B

FIG. 5A. Delayed segmentation, increased secretions, worm-like intervening segments possibly caused by abnormal contractions or the barium column passing through a secretion filled intestinal loop.

FIG. 5B. Same case as 5A, a few minutes later. Note the changing appearance of the dilated and seemingly contracted intestinal loops. The increased fluid content of the bowel is more apparent.

Another form of abnormal distribution of barium seen with hypersecretion is the distorted, slightly thickened, irregular, slightly blunted folds which vary considerably from film to film. These changes can be seen in sprue and also in other instances in which secretions are increased or altered (Fig. 11C).

Hypersecretion. An excessive amount of secretion in the intestinal tract is a constant phenomenon in most cases showing the sprue pattern and especially in those with marked segmentation. Air fluid levels may be seen occasionally during the course of study. The usual homogenous appearance of the barium in the normal small intestine is replaced by barium which presents a coarse granular appearance with areas of flocculation dispersed irregularly in the barium-filled loops. Flocculation is best visualized at the periphery of the segment (Figs. 4A and 4B).

Thickening of the folds. When dilatation of the jejunum occurs, whether due to mechanical or functional changes, the mucosal folds rather than becoming flattened are prominent and seemingly enlarged. In sprue, the *valvulae conniventes* in the dilated jejunum appear remarkably conspicuous (Figs. 2B and 3A). This is in contrast to the usual autopsy findings of a smooth atrophic mucosa. The dynamic state of the bowel is not reflected in the post-mortem findings and it would appear that the prominent mucosal folds produced by an active *muscularis mucosa* are lost.

The thickening of the folds seen in lymphosarcoma and Whipple's disease is more readily understood. The actual infiltration of mucosal and submucosal



FIG. 6A



FIG. 6B

FIG. 6A. Immediate and persistent segmentation, increased secretions, moulage sign.
 FIG. 6B. Same patient as 6A, six months after the initiation of anti-anemic therapy.

layers of the bowel wall produce thickening, stiffening and rigidity of the infiltrated area with accompanying reactive edema.

Transit time. Transit time refers to the interval during which the barium traverses the small intestine and enters the cecum. The average time in adults has been found to be approximately three hours; however, there is a wide range of normal variation. In most of the patients with sprue, transit time varied from three to five hours. In a few, it was less, diminishing to as little as 30 minutes. In four patients, it was as long as six and seven hours. In none was there marked prolongation of transit time. This may be accounted for by the fact that we have used larger quantities of barium than are usually employed and thereby tend to overcome the effect of puddling of barium in a single dilated segment.

Moulage sign. This term has been utilized to describe the roentgen appearance of the jejunum in sprue in which the folds appear to be completely effaced and the barium-filled lumen resembles a tube into which "wax has been poured and allowed to harden" (Figs. 5A and 6A). It was most frequently noted in association with hypersecretion and segmentation (Fig. 6A). In these cases the secretions probably obscured the mucosal markings. In a few cases, no mucosal markings were seen even when there was no dilatation and no hypersecretion. The bowel wall appeared flaccid. The cause of the moulage sign in these cases is not clear (Fig. 8A).

THE APPEARANCE OF THE SMALL INTESTINE IN SPRUE FOLLOWING THERAPY

The impression of improvement in the small intestinal pattern in patients treated for sprue must be evaluated with care because marked variations in the

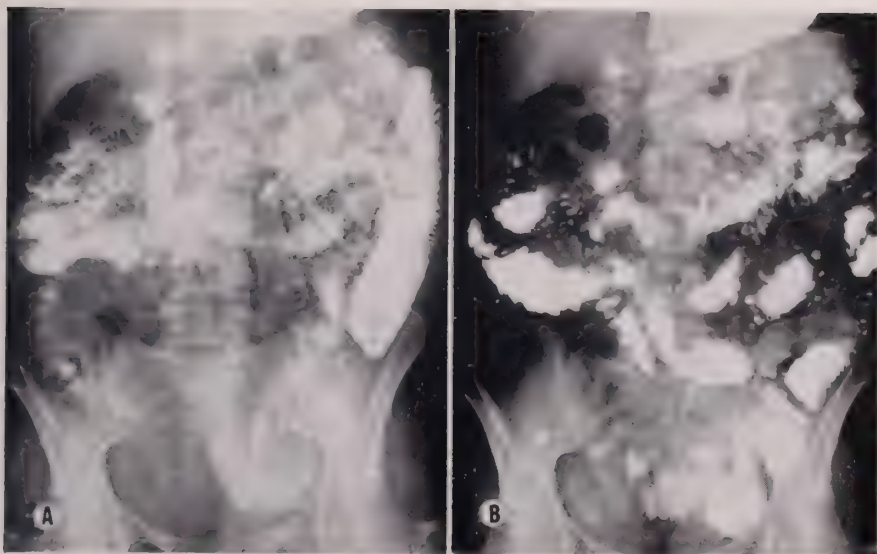


FIG. 7A. Slight dilatation of mid- and distal jejunum.

FIG. 7B. Same patient as 7A, one half hour later, showing delayed segmentation and increased secretions.



FIG. 7C. Same patient as 7A and 7B. After three months of cortisone therapy, the small intestinal pattern shows only minimal alterations in the appearance of the jejunal folds.

appearance of the small intestine in sprue from study to study or even during the course of a single examination may occur. In this study there is a discrepancy between the degree of clinical improvement under therapy and the roentgen changes observed. In only a few instances did the sprue pattern lessen in intensity or disappear.

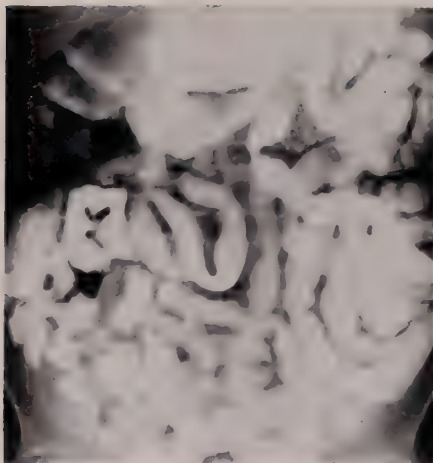


FIG. 8A

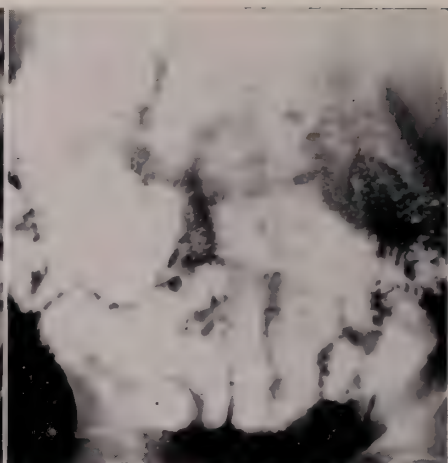


FIG. 8B

FIG. 8A. Moulage phenomenon characterized by absence of mucosal folds and smooth contours of the bowel lumen. Secretions are increased. The necropsy findings, including the small intestine, were normal. Clinically, the patient was considered to have idiopathic sprue.

FIG. 8B. Whipple's disease. Slight dilatation of the mid-jejunum with thickening of the valvulae conniventes. Minimal scattering in the proximal jejunum. Later films showed segmentation, delayed type.

In four of seventeen patients maintained on liver therapy, vitamin B₁₂ or folic acid, the small intestinal pattern returned to normal (Figs. 6A and 6B). Of 22 patients with abnormal small bowel studies receiving steroid therapy, two showed considerable diminution in dilatation and segmentation (Figs. 7A, 7B, 7C). In two others, segmentation and hypersecretion were reduced; however, dilatation persisted. We have had no experience with the effect of a gluten-free diet on the roentgen appearance of the small intestine.

SECONDARY SPRUE

The majority of cases of the malabsorption syndrome are due to idiopathic sprue. There are, however, several groups of diseases which give rise to symptomatic or secondary sprue.

Lymphosarcoma. Most cases of lymphosarcoma do not produce the sprue pattern nor are they associated with the clinical findings of malabsorption. Occasionally there is diffuse infiltration of the submucosa of the small intestine and mesenteric lymphatics producing a sprue syndrome with steatorrhea, excessive fatty acids in the stools and other laboratory evidences of malabsorption (28, 11). In six of 42 patients with lymphosarcoma involving the small intestine, this situation prevailed. In each case, initially, the clinical impression was sprue. Only subsequently at laparotomy or post-mortem examination did the diagnosis of lymphosarcoma become apparent.

The roentgen findings in these six patients were as follows: In four cases, the sprue pattern was seen with segmentation, dilatation, hypersecretion and scat-

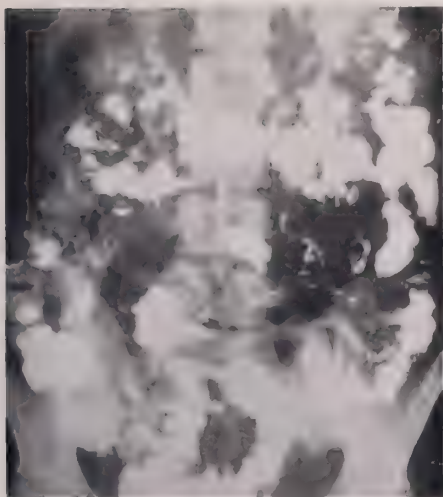


FIG. 9A



FIG. 9B

FIG. 9A. Sprue pattern in lymphosarcoma of the small intestine.

FIG. 9B. Lymphosarcoma of the small intestine with thickening of the bowel wall of the dilated segments.

tering (Fig. 9A). In two patients, in addition to the above findings, there was thickening of the bowel wall suggesting infiltration with tumor (Fig. 9B). It is of interest to note that the sprue pattern was seen only in those patients with marked steatorrhea and increased fatty acids in the stools.

Whipple's disease. Four patients were studied. In three patients, there was clinical evidence of severe malabsorption and, after prolonged observation, the diagnosis of Whipple's disease was made either after biopsy or necropsy. The roentgen findings in these patients were those of the sprue pattern (Fig. 8B). In the fourth patient, who had diarrhea without significant steatorrhea or other evidences of malabsorption, the small intestine, on roentgen study, appeared normal. Again, it is noted that the sprue pattern was seen only in the presence of marked steatorrhea and excessive fatty acids in the stools.

PANCREATIC DISORDERS

In contrast to the marked alterations in the appearance of the small bowel in primary and some cases of secondary sprue, namely Whipple's disease and lymphosarcoma, the roentgen findings in pancreatogenous steatorrhea are essentially normal. On occasion, minimal dilatation of the small intestine may be seen. In one case, slight segmentation was noted. This was in a patient with far advanced carcinoma of the pancreas and carcinomatosis. The lack of changes in the small intestine in pancreatic disorders associated with steatorrhea and malabsorption has been documented in the literature (9).

DIFFERENTIAL DIAGNOSIS

Differentiation should be made between the so-called functional disorders of the small intestine and certain organic diseases. Of these, regional enteritis is the

most important. The inflammatory changes in regional enteritis occur early, are usually severe and extensive. The rigidity of the mucosal folds and lack of distensibility of the bowel lumen indicate the inflammatory infiltrate in the bowel wall. Mucosal ulceration and pseudopolyp formation further attest to the inflammatory nature of the disease process. Delayed segmentation is not seen. Dilatation is not a feature until obstruction supervenes. The involved bowel segments are separated from one another and the remainder of the intestine due to thickening of the bowel wall and intervening mesentery (Figs. 10A and 10B). Regional enteritis may cause malabsorption with steatorrhea; however, the sprue pattern has not been observed in our cases.

Amyloidosis involving the small intestine is uncommon. Thickening and fixation of the mucosal folds by amyloid deposits in the intestinal wall can occur. In one case, thickening of the folds was noted associated with hypersecretion and mild dilatation of the bowel lumen. The roentgen differentiation from sprue, in this instance, could not be made.

Scleroderma may produce small intestinal alterations manifested by dilatation, sacculation and marked hypomotility. In two cases observed, the dilatation of the second and third portions of the duodenum was especially striking. When the disease is sufficiently advanced to produce intestinal changes, the esophageal alterations are characteristic and the roentgen diagnosis is more apparent.

Malabsorption and a sprue-like pattern have been reported subsequent to subtotal gastrectomy (29). On roentgen study in our cases, a normal small intestinal pattern was generally found. A sprue pattern was a most unusual finding. Several patients were observed who showed some small intestinal dilatation following vagotomy with and without subtotal gastric resection; however, segmentation, hypersecretion and other features of the sprue pattern were not seen. In most cases, the dilatation was transient and did not persist following the initial studies.



FIG. 10A

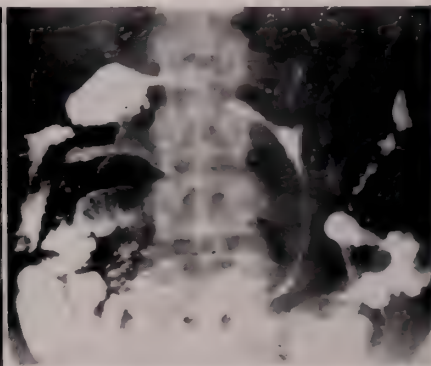


FIG. 10B

FIG. 10A. Non-stenotic form of ileojeunitis. The loops of intestine appear straightened and uncoiled. The folds are thickened, blunted and in some areas, fused.

FIG. 10B. Stenotic type of ileojeunitis. The entire small bowel is involved by alternating areas of constriction and dilatation. The bowel loops are markedly separated.

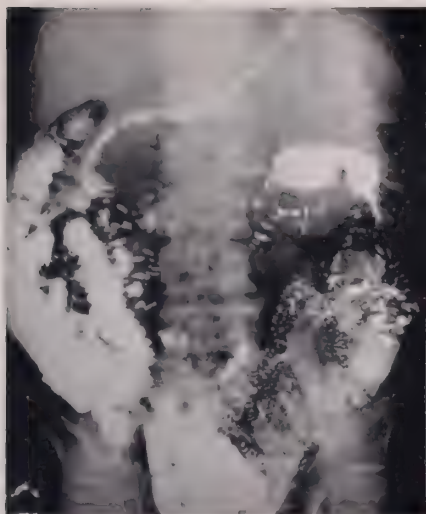


FIG. 11A



FIG. 11B

FIG. 11A. and 11B. Same patient. Minimal dilatation, increased secretions. Slight segmentation and slight thickening of the mucosal folds. The roentgen findings simulate those seen in mild sprue. This patient had toxic hepatitis.

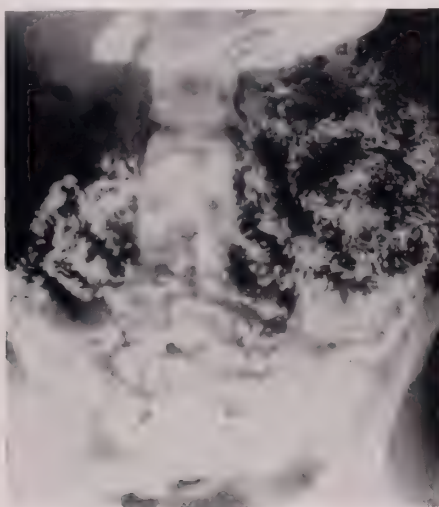


FIG. 11C

FIG. 11C. Increased secretions producing irregular distorted mucosal folds and scattering of the barium column in a patient with mild idiopathic sprue.

Not every patient with sprue shows the marked changes described above. When the changes are mild, the combination of findings of minimal dilatation, delayed segmentation and hypersecretion are still highly suggestive of sprue; however, other diseases of malabsorption, associated with defective fat metabolism, such as cirrhosis of the liver, toxic hepatitis, biliary tract disease, etc. must be included in the differential diagnosis (Figs. 11A, 11B, 11C).

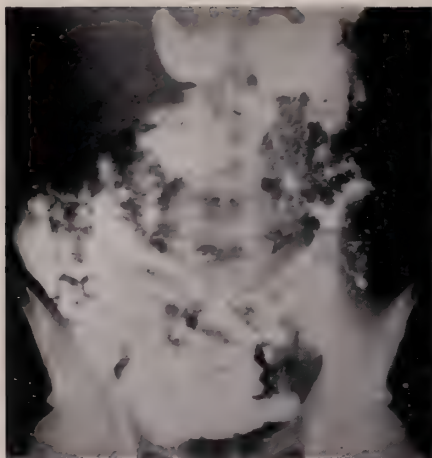


FIG. 12A

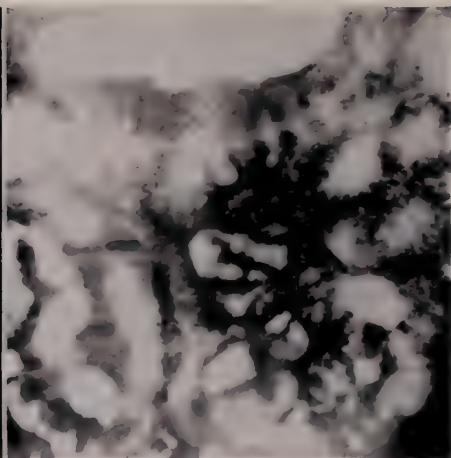


FIG. 12B

FIG. 12A. Thickening and some distortion of the mucosal folds with increased secretions in a patient with allergy.

FIG. 12B. An interrupted column of barium in the small intestine simulating segmentation. Increased secretions. This patient had pyloric obstruction secondary to a duodenal ulcer with intermittent gastric emptying and increased secretions.

The individual components of the minimal sprue pattern, when found alone, are seen not infrequently and are, in themselves, not diagnostic of any specific condition. For example, slight coarsening of the mucosal folds may be seen in allergy (Fig. 12A) and hookworm infestation. Dilatation can be seen following Banthine medication or after vagotomy. Minimal segmentation may occur with pyloric obstruction because of slow intermittent gastric emptying (Fig. 12B) or following administration of small quantities of barium. It may also be seen in emotional disturbances. When the roentgen changes in the small intestine are limited to these minimal alterations, they are difficult to differentiate from one another as they present no obvious distinguishing features and no roentgen diagnosis, as such, can be made.

DISCUSSION

One of the most important roentgen findings associated with the malabsorption syndrome is segmentation of the barium column in the small intestine. The nature of the production of segmentation has been the subject of considerable speculation since it was first described. It was originally considered to be part of an inflammatory process associated with idiopathic steatorrhea, then, as a result of damage to the intramural nervous system of the small intestine or an abnormality in the muscle coat. Many attempts were then made to produce segmentation by the introduction of various foodstuffs into the small intestine. Recently a pattern of segmentation was produced by the addition of mucus, fatty acid and hypertonic solutions into the small intestine. Segmentation was shown to be

due to flocculation of barium within the mucus secretions and could be prevented by using special "non-flocculating" barium mixtures.

If our definition of segmentation is adhered to, namely, segmental distribution of the barium column in discrete masses with hypersecretion and dilatation of the bowel lumen, it is seen only in those cases with severe steatorrhea in which the lipid content of the stool is due to a large amount of fatty acids and neutral fats. It is generally agreed that patients with pancreatic steatorrhea have a normal small intestinal pattern. Steatorrhea, therefore, in itself, would not appear to be the cause of segmentation. However, the lipid content of the stool in sprue and pancreatogenous steatorrhea differ. In the latter, it is due to neutral fats only, occasioned by the absence of the hydrolyzing effect of pancreatic lipase. In sprue, Whipple's disease and those cases of lymphosarcoma associated with steatorrhea, the fat content of the stool is made up of neutral fats and fatty acids. Fatty acids are highly irritating substances and may cause the over-secretion of mucus noted in the intestinal tract.

Although the increased fatty acids and over-production of mucus in the small intestine are probably the major factors, they do not account completely for the presence of segmentation. In patients with sprue, treated successfully, fatty acids in the stools may be returned to normal values; however, segmentation still may persist. One can speculate, then, on what factor or factors continue the production of segmentation. Is it continued hypersecretion of mucus caused by an altered intestinal mucosa? Is it related to abnormal water absorption from the small intestine or to a visceral autonomic nervous system imbalance as shown by Ingelfinger and Moss? Although all these factors may play a role, it appears that the abnormal quality and quantity of the secretions in the intestine caused by the increased fatty acids is the most important single factor in the production of the segmentation pattern.

The mechanism of production of functional changes in the small intestine has been little understood and all variations in the appearance of the small bowel which were considered functional were grouped under the term "deficiency pattern." The inclusion of so many disorders, often because of the presence of one roentgen variation, has caused such a dilution of the term deficiency disorder that it has lost its meaning. It has been recognized for many years that deficiency no longer is the basic factor responsible for the changes. The continued use of this term has prevented the recognition of specific patterns within this all inclusive group. The studies made in this series of patients suggest that the roentgen appearance, when characteristic, is usually associated only with marked steatorrhea (fatty acids) and is most frequently seen in idiopathic steatorrhea (sprue). It is suggested, therefore, that the term "sprue pattern" be utilized for these severe functional alterations. The sprue pattern may also be seen with a slightly lesser intensity in secondary steatorrhea (Whipple's disease and lymphosarcoma).

When minimal functional changes occur in the small intestine, they may be caused by malabsorptive disease. However, these changes are not specific and can also be caused by other diseases unrelated to malabsorption. In describing

these abnormalities, it is suggested that an all-inclusive term such as pattern be avoided and a description only be reported by the radiologist.

ACKNOWLEDGMENT

Acknowledgment is made of permission to reproduce Figures 1B, 3A, 3B, 4A, 4B, 5A, 5B, 6A, 6B, 7A, 7B, 7C, 9B, 10A, which appeared in *Gastroenterology*, 26: 548, 1954, and in *Am. J. Roent.*, 72: 380, 1954 and Figure 1A, *Gastroenterology* 26: 548, 1954, and Figure 12A, *Am. J. Roent.*, 72: 380, 1954.

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MANAGEMENT OF PATIENTS WITH MALABSORPTION SYNDROME

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Treatment of patients with malabsorption syndrome is essentially empirical. Increased knowledge of the fundamental defects may very well lead to a more etiologic approach in the future. It may be stated, however, that present therapy is fairly satisfactory in as much as we have means of correcting, at least to a certain extent, all major manifestations of the disorders grouped under this heading and obtain satisfactory rehabilitation in a great number of patients. In some patients clinical improvement amounting to a "cure" is attained, especially in the tropical variety of sprue or in children with the celiac syndrome. In others, i.e., in patients with non-tropical sprue, complete hematologic remission may be obtained while diarrhea with or without associated symptoms of one or another deficiency may persist and require continuous medication for control.

Primary malabsorption syndrome as seen in idiopathic sprue, tropical and non-tropical, as well as celiac disease of childhood, represents a complex metabolic disorder. It is characterized by diarrhea, steatorrhea, weight loss, anemia and numerous other manifestations resulting mainly, but not exclusively from impaired intestinal absorption. The importance of the dietary management of this disorder has been stressed by many authors, as far back as Gee in 1888 (1). Clinical experience has led gradually to the use of a low fat and high protein diet (2). It became evident that some carbohydrates are better tolerated than others, i.e., monosaccharides are better tolerated than polysaccharides (starches). Thus the standard sprue diet included large quantities of strawberries and bananas (3, 4). Some authors eliminated cereals and obtained excellent results in celiac disease (5). In recent years emphasis has been focused on the gluten content of wheat and rye (6). Gluten-free starch is apparently well tolerated. Details of the development of this knowledge will be given in the section on dietary management.

Other specific measures for the treatment of sprue have been searched for. It appears that physicians in China and in Ceylon knew many centuries ago of the usefulness of liver in the treatment of sprue. In 1927 after the introduction of liver therapy for pernicious anemia, Bloomfield and Wycoff treated similarly a case of sprue with macrocytic anemia and observed excellent clinical improvement (7). Crude liver extract appears to be superior to the highly purified liver preparations (8). Since their introduction, folic acid and vitamin B₁₂ have been used extensively. Folic acid appears to be more effective in patients with tropical sprue (9). Similar results have been reported with folinic acid (10).

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In patients with non-tropical sprue the clinical response to the dietary management supplemented by the above described drugs may result in correction of the anemia and variable control of other manifestations of the malabsorption syndrome. There are, however, numerous patients in whom this control is not adequate. Additional measures are then employed, such as the administration of calcium, iron and potassium salts, vitamin B complex, vitamins C, D or K. At times antibiotics have been used with good results especially in the tropical variety (11). Other measures, such as transfusions or the administration of serum albumin or plasma may be life saving.

In refractory cases, responding poorly or only partially to the above described measures, the administration of corticosteroids or corticotropin has induced a clinical remission in the majority of patients observed by us and independently by others (12-18). The plan for management of patients with idiopathic sprue which is used at The Mount Sinai Hospital will be described.

DIETARY MANAGEMENT

Since the major manifestations in the malabsorption syndrome are related to impaired handling of fat and polysaccharides, the basic regimen consists of a high-protein, low-fat diet with moderate amounts of carbohydrates preferably given as monosaccharides. It centers around lean meat, egg whites, cottage cheese, skimmed milk, bananas and strawberries. The amount of food is gradually increased in proportion to the patients' tolerance. To avoid monotony it is imperative to guide the patient and teach him to prepare a variety of combinations of the above simple ingredients to obtain more normal appearing meals. A good selection of recipes can be found in an article previously published from this hospital (19).

High protein appetizers can be prepared by adding two tablespoons of cottage cheese or egg whites to tomato juice, by blending chopped liver with an egg white and tomato juice, or by preparing dishes consisting of cottage cheese, bananas and melba toast crumbs.

Soups can be enriched with egg white, Parmesan cheese or ground beef. Sea food chowders can be made with skim milk, oysters, clams or mussels.

Lean meats and fish should be chosen and trimmed to keep the fat as low as possible. Meat, fish and poultry can be broiled, boiled or roasted. Combinations of ground beef, banana flakes and cottage cheese make an appetizing meat loaf.

Vegetables and salads should be low in carbohydrates. Frozen and molded salads can be prepared with cottage cheese and gelatin.

Desserts can be prepared using bananas and strawberries with gelatin, egg white or cottage cheese. Creamy type puddings can be prepared with skim milk and the allowed fruits. Saccharin, lemon juice, vanilla or other flavors can be used to make these dishes more attractive.

As the general condition improves more food items are introduced, leading gradually to a bland type of diet. But even then it is important to avoid consumption of large amounts of fat or cereals.

GLUTEN-FREE DIET

A new approach to the dietary management has evolved in the past few years. Studies in Holland (20), confirmed by observations in England (21-23) and in this country (24), have led to the observation that, in a great number of children with celiac disease and a certain number of adults with sprue, good clinical control has been achieved with gluten-free diets that contain otherwise liberal amounts of fat and starch. The deleterious effect of wheat flour was attributed to its gluten content and more specifically to the gliadin fraction. The administration of wheat starch (free of gluten) did not result in any harmful effect. This approach seemed to be less successful in adults with sprue. The question has been raised whether all clinical entities grouped under the heading of idiopathic sprue represent the same basic defect. One may reason that some patients have a specific sensitivity to gluten and will respond favorably to the elimination of this element. This diet has the advantage of increased variety since the only foods to avoid are the wheat and rye products. Obviously great care is needed to ascertain that even small amounts of such foods are avoided. Carbohydrates may be taken in form of bread made with wheat starch (gluten-free), rice flour, corn meal, potato starch or soy beans. There are numerous cereals on the market made with corn or rice to allow variety. The diet includes all fruits, vegetables and juices, all meats and meat substitutes as well as liberal amounts of fat. Desserts may be made of fruits, corn starch, rice, tapioca, custard, gelatin and sherbets. Some authors allow milk and ice cream. Our experience with this type of diet is limited but good results have been reported by many authors (21-24). Table I presents list of foods allowed and to be avoided in the gluten-free diet and Table II shows a sample menu.

DRUG THERAPY

Certain drugs have become an essential part of the management of patients with malabsorption syndrome.

Liver extract, preferably the crude preparation, is given parenterally. It must be given in larger doses than for pernicious anemia, 2 to 4 ml. daily by intramuscular route during the acute phase of relapse, later on once or twice weekly depending on the clinical improvement.

Folic acid can be administered both orally and/or parenterally in doses of 10 to 30 mg. daily. Although it appears to be extremely useful and can control the anemia and the diarrhea of patients with tropical sprue, it should be used very cautiously in patients with lesions of the central nervous system. Large doses of vitamin B₁₂ should be given simultaneously.

Folinic acid (leucovorin, citrovorum factor) is effective during the acute phase in intramuscular doses of 3 mg. daily. It may be followed by weekly injections of the same dose after clinical improvement is achieved.

Vitamin B₁₂ can result in striking hematologic and clinical response in doses of 100 µg. given parenterally. Maintenance doses of 30 µg. weekly are often sufficient to maintain a satisfactory hematic control. In the presence of central nervous system involvement daily parenteral doses of 1 mg. are indicated.

TABLE I

Gluten free diet

This diet is free from cereal proteins except those found in rice and corn

Foods Allowed	
Milk.....	Two glasses or more, flavored if desired, more for children.
Eggs.....	One to two a day.
Meat, fish, or poultry.....	Two medium servings daily (not breaded, creamed or served with thickened gravy, or bread dressings otherwise prepared as desired).
Cheese.....	As desired.
Bread.....	Made from rice, corn, soy bean and gluten-free wheat flour only. Popcorn, potato chips, Fritos, Cheetos.
Cereals.....	Corn flakes, cornmeal, hominy, rice, Rice Krispies, Puffed Rice, Sugar corn pops.
Fat.....	Margarine, true mayonnaise without wheat products, butter, all oils except wheat-germ oil.
Vegetables, potatoes.....	As desired, except creamed. Rice may be substituted occasionally for potatoes.
Fruits.....	As desired.
Soups.....	All clear and vegetable soups; cream soups thickened with cream, cornstarch or potato flour only.
Desserts.....	Jello, fruit Jello, ice or sherbet, homemade icecream, custard, Junket, rice pudding, cornstarch pudding (homemade) or <i>blanc mange</i> if thickened with cornstarch.
Beverage.....	Milk, fruit juices, ginger ale, cocoa, coffee (made from ground coffee), tea, carbonated beverages.
Sweets.....	Sugar (white or brown), molasses, jellies and jams, honey, corn syrup.

Foods Omitted	
Meat, fish and poultry.....	Meat patties or meat loaf made with bread or bread crumbs, croquettes, breaded meats, fish or chicken, bread stuffing, chili con carne and other canned meats, cold cuts unless guaranteed pure meat.
Gravies, sauces.....	All gravies or cream sauces thickened with wheat or rye flour.
Bread.....	All bread, rolls, crackers, cake and cookies made from wheat or rye; Ry-Krisp, muffins, biscuits, waffles, pancake flour and other prepared mixes, rusks, zweiback, pretzels, other products containing oatmeal, barley or buckwheat; breaded foods, bread crumbs.
Cereals and cereal products.....	All wheat and rye cereals, wheat-germ, barley, oatmeal, buckwheat (<i>kasha</i>), noodles, macaroni, spaghetti, dumplings.
Fats.....	Commercial salad dressings except pure mayonnaise.
Vegetables.....	Any prepared with cream sauce or breaded.
Soups.....	All canned soups except clear broth; all cream soups unless thickened with cream, cornstarch or potato starch.
Desserts.....	Cakes, cookies, pastry, puddings and commercial ice cream; All homemade puddings thickened with wheat flour.
Beverages.....	Postum, malted milk, Ovaltine, instant coffee, beer, ale
Sweets.....	Commercial candies containing cereal products.

WARNING: Check all labels for presence of wheat or rye flour.

TABLE II
Sample Menu

Meal Plan		Servings	
		Weight (gm.)	Household measure
Breakfast			
Fruit.....	Orange	100	1 medium
Egg.....	Soft cooked	50	1
Cereal.....	Corn flakes	20	1 serving
Milk.....	Milk	240	1 glass
Bread.....	Rice bread	20	1 slice
Butter.....	Butter	5	1 pat
Coffee.....	Coffee	200	1 cup
Milk.....	Milk	60	1 pitcher
Sugar.....	Sugar	15	1 tablespoon
Luncheon			
Soup.....	Clear broth	150	1 cup
Protein dish.....	Cottage Cheese	60	$\frac{1}{4}$ cup
Salad.....	Lettuce	30	2 leaves
	Tomato	100	1 medium
Dressing.....	French dressing	6	2 teaspoons
Bread.....	Rice bread	40	2 slices
Butter.....	Butter	10	2 pats
Beverage.....	Milk	240	1 glass
Dessert.....	Custard	100	1 cup
Dinner			
Meat.....	Roast beef	90	3 ounces
	Pan gravy	30	2 tablespoons
Potato.....	Potato	100	1 medium
Vegetable.....	Baked squash	100	1 serving
	Spinach	75	1 serving
Bread.....	Rice bread	20	1 slice
Butter.....	Butter	10	2 pats
Dessert.....	Homemade ice cream	60	1 serving
Beverage.....	Coffee	200	1 cup
Milk.....	Milk	60	1 pitcher
Sugar.....	Sugar	15	1 tablespoon

Vitamin B concentrates in form of injections of vitamin B complex are often useful. Oral administration may, however, give excessive bloating.

Iron therapy is indicated in patients with microcytic hypochromic anemia. At times oral iron therapy may be inadequate, since the intestinal absorption of this element may be markedly impaired. Parenteral administration of adequate doses may produce dramatic results, as may be seen from the case presented in Figure 1.

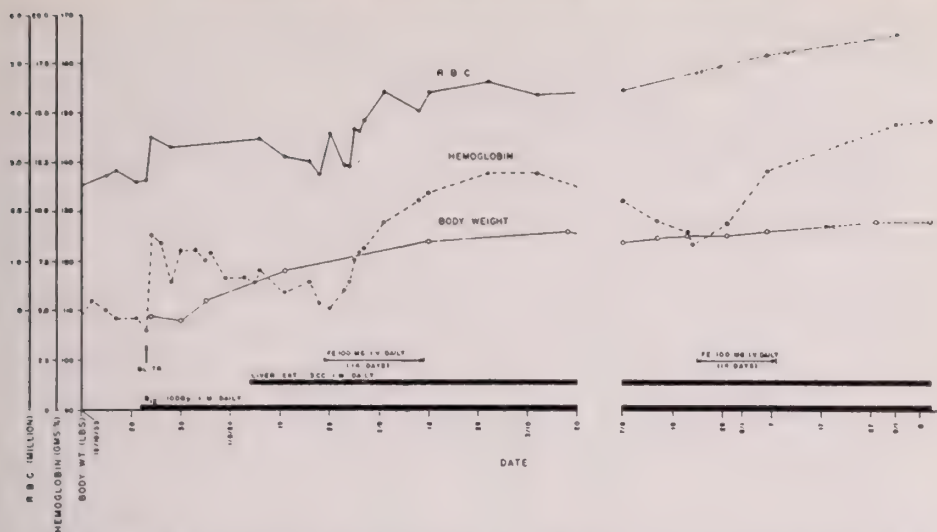


FIG. 1. Effect of intravenous iron therapy in a patient with non-tropical sprue and microcytic hypochromic anemia. Note the prompt effect of iron administration (two courses) on the blood count in contrast to that of prolonged parenteral therapy with vitamin B₁₂ and liver extract. (Ref. 18)

Additional supplements must be given to patients who present other deficiencies. Hemorrhagic manifestations caused by hypoprothrombinemia respond to the parenteral administration of vitamin K. In the presence of associated hepatic damage large amounts of fresh blood may be indicated. Marked hypoproteinemia may be corrected to a certain extent by the administration of large doses of salt-free albumin or plasma. This effect is usually transient and more lasting results may be obtained by steroid therapy (see later). Hypocalcemia and tetany require administration of large doses of calcium salts, orally and/or parenterally. Osteomalacia and osteoporosis may be helped by large doses of vitamin D and testosterone. This form of therapy is discussed elsewhere in the symposium (25). Some patients, especially those with marked lassitude, may benefit from the administration of potassium salts.

Careful observation of the patient, painstaking attention to details and prolonged use of various combinations of drugs will usually result in satisfactory control of the malabsorption syndrome and allow the patient to lead a fairly normal life. A certain equilibrium may then be established that will permit the omission of some drugs for varying periods. At the slightest indication of recurrence it is essential to resume the full therapeutic program. After various periods of time some patients may develop various degree of resistance to these measures.

RESULTS OF DRUG THERAPY

Out of a larger number of patients 94 were selected for detailed analysis. The average observation period of this group was 5.2 years. Clinical data and diagnostic criteria are presented elsewhere (26). Management can be described as a

systematic and gradual application of various therapeutic measures guided by the patient's response. Attempt was made at first to control the manifestations of the malabsorption syndrome by diet alone. When the symptoms and signs were severe, and this applied to the majority of our patients, additional therapeutic measures were introduced as rapidly as compatible with the principle of evaluating the efficacy of each preceding step. Only rarely, however, was the clinical picture so alarming that many drugs were given immediately and separate analysis was impossible.

The therapeutic response was recorded in the following manner: (a) remission (b) full control (c) partial control (d) no change (e) fatal termination.

Remission was defined as disappearance of all clinical manifestations, not only during the treatment period but also during a prolonged follow-up without treatment. After cessation of all medication the patient could tolerate a practically free diet. Only six patients could be placed in this group. Five of these were Puerto Ricans and one Jewish. Five had received liver extract and one was given liver extract and vitamin B₁₂. It is possible that improved dietary habits and perhaps living conditions played a significant role in maintaining clinical remission once the acute phase or the manifestations of the syndrome were brought under control.

Full control was defined as achievement of satisfactory control of all major manifestations of the malabsorption syndrome, while under continued therapy. This was observed in 32 patients. Seventeen had received liver extract with folic acid and two received vitamin B₁₂ in addition to the above. Some patients of this group responded originally to the standard therapeutic regimen but became refractory to it after months or years. Others proved to be therapy-resistant from the beginning and required steroids. Corticotropin or one of the cortisones were then administered as will be discussed later.

Partial control. This group never achieved full control of all the manifestations of the malabsorption syndrome. The degree of control varied from patient to patient. At times some manifestations were fully controlled, while other evidences of malabsorption persisted. There were also fluctuations in the degree of control, perhaps related to seasons or to emotional factors not always clearly understood. This group of 37 patients was the largest in our series. The drugs used in this group were as follows: diet with only vitamin supplements in one patient; diet with vitamin supplements and liver extract in 13 patients; all these factors plus folic acid in one patient and with vitamin B₁₂ in five other patients. Seventeen patients of this group were given various steroids and will be discussed later.

No change. Six patients failed to respond to the forms of therapy employed. One was treated with diet alone; two received diet with liver extract; one received folic acid in addition to these therapeutic agents and two did not respond to all these measures even when supplemented with corticosteroids.

Fatal termination. Thirteen patients died during or after their treatment at the hospital. Eight received diet with liver extract and folic acid. One received vitamin B₁₂ in addition. Four received steroids, three of these were treated in the terminal stages of their disease; the fourth had responded favorably for two

years but died subsequently despite continued therapy; these four cases will be discussed later.

STEROID THERAPY

The debatable role of the adrenal cortex in intestinal absorption (12) suggested the use of corticosteroid therapy in refractory cases of the malabsorption syndrome. Satisfactory results have been obtained with this form of therapy which has been used in this hospital since 1950 (12, 15, 16, 18). A total of 33 patients with refractory sprue treated with corticotropin or the cortisones have been selected for analysis. Of these, 30 patients have been observed for periods from six months to six and a half years. One patient presented elsewhere in this symposium (26) was not available for follow-up studies.

Dramatic results within a few hours have been obtained during the "acute" phase of the disease by intravenous administration of corticotropin or hydrocortisone. The usual approach was administration of relatively large doses of either cortisone, hydrocortisone, prednisone or prednisolone orally with gradual reduction in dosage depending on the clinical improvement. The initial daily dose was usually 100 mg. of cortisone, 80 mg. of hydrocortisone free alcohol and 50 to 60 mg. of prednisone or prednisolone. This was given orally in divided doses. ACTH was usually injected intramuscularly (80 to 100 mg. in two doses 12 hours apart). The initial daily dose was usually maintained for eight to ten days. Since improvement was often manifest within a few days it was possible to start reducing the dosage after the first week of therapy. This reduction was done by weekly decrements of 10 to 20 mg. until the maintenance dose was reached. The main guiding features were the number of stools, appetite, weight and well being.

Since our purpose has always been to establish the minimal dose of steroids needed to maintain clinical control, we have often "titrated" the patients by gradual reduction of the daily dose to such low levels as 15 mg. of cortisone or 5 mg. of prednisone daily, with continuous, careful observation of all symptoms and signs. In the process of "titration" recurrence of some of the manifestations of sprue was observed. It was then necessary to raise the dose of the drugs to somewhat higher levels, still remaining within "safe limits" to allow long term administration.

Table III shows the data concerning prolonged steroid therapy in 30 patients. Seven patients have been on almost uninterrupted therapy for five years or longer, six patients from four to five years, eight from three to four years, and nine patients less than three years, but not less than six months. During the initial period of steroid therapy the standard sprue diet remained unchanged, except for limitation of the salt intake to less than 2 gm. per day. The diet was then gradually liberalized to a bland mixed diet, with some limitation of fats, coarse vegetables and fruits. Supplements of calcium and potassium salts were often given. The standard anti-anemic drugs were always continued (liver extract, folic acid and vitamin B₁₂). If required, iron salts were also given orally or parenterally. With the initial larger doses of corticotropin or cortisone fluid

retention was sometimes encountered and treated with mercurial diuretics. This phenomenon was seen less often with prednisone or prednisolone. On several occasions, when a patient appeared fully controlled with small doses of steroids, attempts were made to discontinue these hormones. This was followed within relatively brief periods by partial recurrence of manifestations of the malabsorption syndrome heralding the onset of relapse. Resumption of steroid therapy at a

TABLE III
Results of Steroid Therapy in 29 Patients

Case No.	Sex	Age	Duration of disease prior to observ. (yrs.)	Aver. daily maint. dose, (mg.)				Duration of therapy (mons.)	Result	Remarks
				ACTH	E	F	P			
1	M	36	2				30	14	4+	
2	F	42	16			30	10	48	4+	Tetany
3	F	30	10	60/20		50/30		70	4+	Volvulus of cecum
4	M	37	10	50	75	30	15	60	4+	Marked hypoproteinemia
5	F	39	11			40	15	60	4+	
6	M	57	2			40		45	3+	Hemiplegia
7	F	59	1	20/wk.		30	30	45	3+	Osteoporosis, tetany
8	M	43	11				10	36	4+	Combined system disease
9	F	55	1			25	10	45	4+	
10	F	37		40/20			10	36	3+	
11	F	43	2	60	50	20	10	62	4+	
12	F	60	10	50	50	20		76	3+	Hemorrhagic phenomena
13	M	40	9	20	60	40		60	3+	
14	F	41	13	40				26	4+	Diabetes
15	F		6			40		45	4+	
16	F	63	3				20/5	14	3+	Fractures
17	M	56	1				12	10	4+	
18	F	47	11	56		40	15	26	4+	
19	F	36	8	20	50	15	10	48	4+	
20	F	46	40			20		40	4+	
21	M	41				40/15	20	8	3+	Interrupted for 2 yrs.
22	F	65	2		50	20		48	4+	
23	F	60	9			40	25	48	4+	
24	M	50	17	60	75	20	15	54	4+	Osteoporosis, hemorrhagic phenomenon
25	F	28	6	40	50	40	20	78	4+	
26	F	40	7			30	7	48	4+	
27	F	41	4				10	8	4+	
28	M	26	8			40	20/15	18	4+	
29	M	35	1	50	50			36	3+	Died

E = cortisone; F = hydrocortisone; P = prednisone or prednisolone.

somewhat higher initial dose promptly controlled the recurrence. It has been our routine to interspace prolonged cortisone therapy with short courses of corticotropin in order to combat possible inactivation of the adrenal cortex. Daily injections of ACTH were used for one week or ten days. Recently we have been employing a different technique. The patient continues to take orally one of the cortisones at the established maintenance level and receives in addition

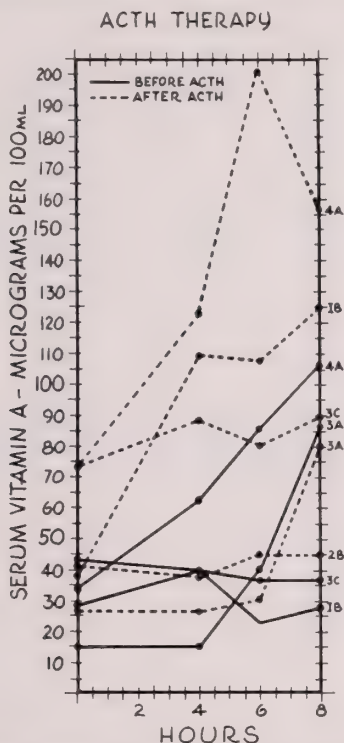


FIG. 2. The effect of ACTH therapy on vitamin A tolerance test in patients with sprue. The uninterrupted curves represent the pre-treatment tests while the interrupted curves represent the tests performed during or soon after ACTH therapy. The numbers in arabic followed by capital letters (1A, 1B) designate patient and course of therapy. No pre-treatment test was performed before course 2B (Ref. 12).

weekly or bi-weekly injections of ACTH, usually 20 units. The usefulness or advantages of this approach is difficult to evaluate.

RESULTS OF STEROID THERAPY

Clinical remission was observed in 28 patients. The extent of this remission varied from patient to patient. The important clinical changes were increase in well being, increase in appetite that at times became ravenous often leading to considerable gain in body weight, the subsidence of diarrhea, and reduction in steatorrhea. There was laboratory evidence of improvement, namely, increase in serum albumin, serum calcium, fasting carotene and vitamin A levels. Improved oral dextrose tolerance tests and vitamin A tolerance tests were also noted (Fig.

2). Symptoms related to hypoalbuminemia and hypocalcemia, such as edema or tetany, disappeared with the correction of the blood abnormalities. At times radiologic evidence of improvement (disappearance of the sprue pattern) was noted. Extensive case histories and chemical and roentgen studies have been published previously (12, 15, 16, 18, 27).

For tabulation purposes patients were divided according to the over-all therapeutic response over this extended period of observation. Those who showed significant clinical and laboratory evidence of improvement for prolonged periods of time were classified as four plus. These patients were leading a normal life for all intents and purposes but had to continue the maintenance doses of one of the steroids. At times the administration of drugs was interrupted for several weeks, but signs of relapse necessitated resumption of steroid therapy. They could tolerate a practically free diet and pursue their occupations. A total of 20 patients were considered to belong in this group.

The results obtained in eight patients were classified as three plus. Despite good clinical improvement they were more apt to show minor symptoms or signs of relapse either after some food indiscretion or after too rapid a reduction in the dose of the steroid. They were easily fatigued and less able to pursue a normal life.

One patient (Case 4) was classified as two plus. His diarrhea, steatorrhea, appetite and sense of well being were fairly well corrected when given steroids, but the main manifestation of his disease, marked hypoalbuminemia, was not changed. One patient (Case 29 of Table III) died and will be discussed later.

No instance of cure or full remission was observed. Symptoms invariably recurred after various time intervals when the steroids were discontinued. Steroid therapy was discontinued at some time in all patients, but all of them relapsed and required resumption of steroids.

REPORT OF CASE

Case 25 (Table III) is presented to illustrate the long term management of a patient with non-tropical sprue. The clinical course before steroid therapy and the effects of cortisone and ACTH during 1950 and 1951 were reported previously (12). Various steroids have been employed during the past six and a half years and have resulted in the rehabilitation of this patient.

The patient, a white, Jewish woman, was born in New York City in 1921. She had never travelled abroad and gave no personal or family history of nutritional or intestinal disorders. During childhood, she was considered to be underweight and sickly and suffered from attacks of frequent epigastric pressing pains, occasionally associated with vomiting. Her growth and development was otherwise fairly normal. At the age of 17 years she reached a peak weight of 116 pounds. At age 20, on her wedding night, the patient experienced an acute attack of abdominal cramps associated with eight to ten non-bloody, watery stools. These symptoms persisted for two weeks and subsided spontaneously. Shortly after her marriage the patient became pregnant. Six weeks after delivery, in the spring of 1942, she had her second attack of abdominal cramps and diarrhea consisting of three to four loose or semi-formed, foul-smelling, non-bloody stools. This attack again lasted two weeks and subsided without specific therapy. Similar attacks occurred regularly each spring for the next

five years, were associated with a weight loss of five to ten pounds and increased gradually in intensity. The diagnosis of non tropical sprue was made in the spring of 1949 and the patient was treated with injections of liver extract, vitamin B complex and antispasmodics. In June 1949 she was hospitalized because of an acute exacerbation with marked weight loss and dehydration necessitating transfusions, glucose and saline infusions, in addition to treatment with folic acid and vitamin B₁₂. Two months later the patient was readmitted because of an exacerbation of diarrhea and the onset of amenorrhea. Her weight was 83 pounds. She appeared pale and cachectic. The abdomen was somewhat distended. There was a mild normochromic anemia. The prothrombin time was 120 seconds (control 11 seconds). The stool contained large amounts of fatty acid crystals. Serum albumin was 2.9 and serum globulin was 1.7 gm. per 100 ml. The oral glucose tolerance test revealed a flat absorption curve. Gastric analysis revealed free acid. Pancreatic secretion studies before and after the administration of secretin showed a normal volume flow and bicarbonate concentration but a somewhat reduced amylase concentration. Radiologic studies showed dilatation of several loops, segmentation and scattering of barium in the small intestine. Despite intensive and prolonged standard therapy, the patient ran a progressively deteriorating course during the next five and a half months (Fig. 3). Diarrhea persisted, ascites and leg edema appeared. Her weight fluctuated between 73 and 87 pounds. There was one episode of hypocalcemic tetany and transient manifestations of purpura. Administration of

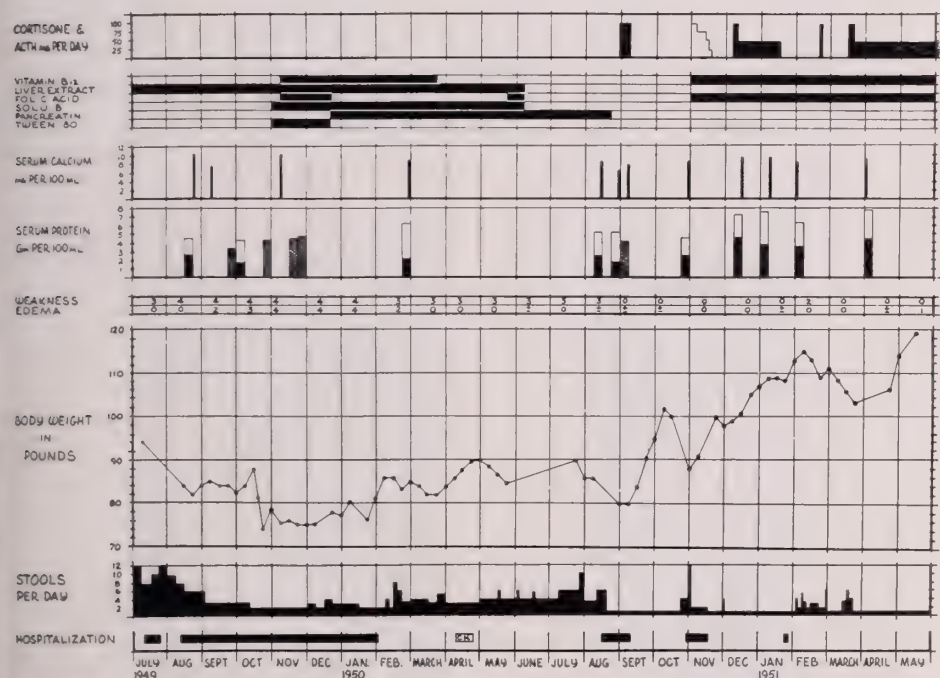


FIG. 3. The effect of ACTH and cortisone treatment on a therapy-resistant sprue patient. The white block indicates the dose and duration of ACTH administration and the black blocks indicate the dose and duration of cortisone therapy. The total serum proteins are represented by cross-hatched blocks; whenever the serum albumin and globulin fractions were determined they were represented as the black and white areas of a block respectively. C.H. represents convalescent home. ACTH and cortisone treatment resulted in a decrease in the number of stools, an increase in body weight and an improvement in the sense of well-being. Exacerbations of symptoms followed cessation of therapy. Prolonged cortisone therapy resulted in a striking weight gain and was associated with the return of the serum calcium and albumin to normal levels. (Ref. 12.)

antibiotics, Sulphatholidine and Chloromycetin had but transient beneficial effects. Because of persistence of severe symptoms and resistance to all known forms of therapy she was readmitted in August 1950 for a trial with cortisone. Clinical findings and laboratory data were similar to those observed on earlier admissions. Total fecal fat was 40.6 per cent of the dry fecal weight. Serum calcium varied from 6.5 to 8.5 mg. per 100 ml. Repeated oral glucose and vitamin A tolerance tests revealed flat absorption curves. Cortisone therapy was instituted with daily intramuscular injections of 100 mg. for ten days. Diarrhea disappeared promptly; appetite and good consumption improved, resulting in a weight gain of 23 pounds. About five weeks after discontinuation of cortisone therapy the patient had a recurrence of diarrhea with loss of 13 pounds. She was readmitted in October 1950 for a 12 day course of ACTH. Again there was a prompt disappearance of diarrhea and an increase in appetite and sense of well being with gain of 11 pounds. In December 1950, after another mild clinical relapse, the patient was started on a prolonged course of steroid therapy. This has been continued to the present (February 1957) with occasional brief interruptions. By May 1951 her weight reached 119 pounds and she was capable of performing part-time secretarial work in addition to her household duties (Fig. 4).

Frequently attempts were made to re-evaluate the patient's need for the various steroids in order to maintain good appetite, a sense of well being and regular bowel movements. At times as little as 15 mg. of cortisone daily was sufficient for extended periods. On other occasions, however, the dose had to be raised to as much as 75 mg. of cortisone daily. The larger doses were associated on occasion with marked constipation. The hemotologic status remained normal. Serum protein and calcium returned to normal values in 1951. Prothrombin concentration was kept adequate with vitamin K administered either orally or parenterally. The effect of steroid therapy on vitamin A tolerance tests is illustrated in Figure 5. The radiological appearance of the small intestinal tract was considered normal after one year of prolonged therapy, and remained so during follow-up studies. During her last admission to the hospital (November 1955) the oral dextrose tolerance test revealed



FIG. 4. Case 25, Table III. A. Taken in 1947, body weight approximately 80 pounds. B. Taken in 1951, after ten months of steroid therapy, body weight 129 pounds.

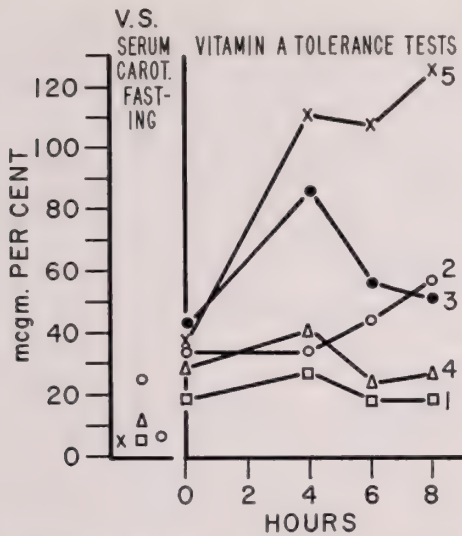


FIG. 5. Test 1 was performed on Aug. 17, 1950 before institution of cortisone therapy; tests 2 and 3 on Sept. 5, 1950 and Sept. 20, 1950 during cortisone therapy; test 4 was performed on Oct. 30, 1950 forty days after discontinuation of cortisone and prior to institution of ACTH therapy; test 5 was performed on Nov. 13, 1950 after 2 weeks of ACTH therapy.

Note improvement of vitamin A absorption under cortisone, indicated by higher serum vitamin A levels during the tolerance tests, the return to the flat curve 6 weeks after discontinuation of cortisone, and the decided improvement with ACTH.

a normal curve: 84, 126, 159, 129 and 132 mg. per 100 ml. in the fasting, 30, 60, 120 and 210 minutes specimens. The vitamin A tolerance test was normal (Fig. 3). Blood studies were as follows: serum albumin, 4.3 gm. per 100 ml.; serum globulin, 3.1 gm. per 100 ml.; serum calcium, 10.5 mg. per 100 ml.; phosphorus, 3 mg. per 100 ml.; total cholesterol, 210 mg. per 100 ml.; cholesterol esters, 175 mg. per 100 ml.; serum sodium, 147 mEq. per liter; serum potassium, 3.9 mEq. per liter. The stool was formed, brown and contained no fat on microscopic examination. Total fat was 24.5 per cent of dry fecal fat, with neutral fat 10 per cent and fatty acids 14.5 per cent.

During the six and a half years of steroid therapy the patient was maintained mainly on oral cortisone; however, in 1950 she received it by the intramuscular route. The injections were discontinued when the patient developed a gluteal abscess and the oral preparation became available. Once in 1950, and at irregular intervals afterward, this medication was interrupted by brief courses of ACTH.

During 1951 and the spring of 1952 the patient's symptoms were well controlled with an average dose of 45 mg. of cortisone daily. In May 1952 a trial with oral hydrocortisone acetate, 100 mg. daily for 20 days, resulted in reappearance of the diarrhea within two weeks and caused a weight loss of eight pounds (from 125 to 117). This was controlled by resuming cortisone in daily doses of 100 mg. for four days. This dose was then gradually reduced to 50 mg. daily. Later in 1952 and during the first two months in 1953 the daily dose of oral cortisone was 25 mg. and the general condition of the patient remained good. In March 1953, during a period of severe illness of one of her children, diarrhea and nausea reappeared and the dosage was raised to 100 mg. daily for three days and then gradually reduced to 75 mg. and then to 50 mg. After two weeks it was possible to return to the previous maintenance dose of 25 mg. of oral cortisone daily. Other compounds proved to be equally satisfactory. Prednisone in oral doses of 10 to 15 mg. per day controlled all the manifestations of the

syndrome from May to October 1955. After a brief course of ACTH (20 units of ACTH gel daily for one week), prednisolone in daily oral doses of 10 to 20 mg. was used. The patient believed that her control with this drug was less satisfactory. Therefore cortisone was resumed in March 1956 in somewhat larger doses (75 mg. daily). For the past year the patient has remained on oral cortisone with satisfactory control of most of the manifestations of sprue. She presents, however, two complaints. The first one is referable to vague nervous manifestations (occasional tremor and paresthesias in either hand). The other complaint is of recurring attacks of right upper quadrant pain, at times requiring injections of narcotics. Careful investigation, including roentgen studies of the gastrointestinal tract, the gall bladder and the kidneys, failed to reveal any organic abnormalities that could explain these episodes. With the exception of these two complaints the patient has had a normal life during these six and a half years, working part-time as a medical assistant in addition to her household duties.

This case illustrates the type of patient classified as primary non-tropical sprue resistant to prolonged standard therapy. The administration of cortisone, corticotropin, prednisone and prednisolone over six and a half years resulted in full control of manifestations of the malabsorption syndrome and in the rehabilitation of the patient. It also depicts the various problems encountered during long term management of sprue with steroid therapy.

FATALITIES OBSERVED DURING STEROID THERAPY

Four patients died while receiving steroids. One patient, (Case 29 of table III) responded satisfactorily for two years (15). During the third year of steroid therapy he developed repeated gastrointestinal hemorrhages that persisted after a subtotal gastrectomy. This part of his course and the autopsy findings are described elsewhere (28). There were multiple ulcerations and erosions of duodenum, jejunum and ileum. The jejunum presented a perforated ulcer contiguous with a sub-diaphragmatic abscess. There were also several areas of thickening of the jejunal wall with evidence of jejunitis. It is difficult to evaluate the role of the steroid therapy in the development of these lesions since bleeding and unexplained fever were present before the start of steroids.

The second patient was included in a previous report (Ref. 15, Case 2). A 59-year old Irish woman with sprue symptoms of 15 years' duration, persistent diarrhea and severe hemorrhagic manifestations had three brief courses of therapy with steroids with minimal response. She succumbed to a bilateral pneumonia at another hospital one month after cessation of cortisone therapy. The autopsy findings are reported elsewhere in this symposium (Ref. 29, Case 7).

The third patient, a 66-year old woman, was admitted for the seventh time on December 7, 1951. The diagnosis of sprue was made eight years earlier. The repeated admissions were motivated by either severe diarrhea, hemorrhagic manifestations or symptoms related to hypoalbuminemia or hypocalcemia. She proved refractory to standard therapy that included liver extract, folic acid and vitamin B₁₂. The final admission was for extreme weakness, abdominal pain, anemia, extensive decubitus ulcer and incontinence of feces. She was emaciated and pale. There were skin ecchymoses over arms and thighs. The significant laboratory data were: hemoglobin, 9.1 gm. per 100 ml.; RBC, 3.3 millions per cu. mm.; WBC, 8000 per cu. mm.; platelets, 120,000 per cu. mm.; prothrombin time, 21

seconds (control 12), which increased later to 30 seconds (control 13); serum albumin, 218 gm. per 100 ml.; serum globulin, 2.8 gm. per 100 ml.; blood sugar, 60 mg. per 100 ml., with a flat oral dextrose tolerance test; serum vitamin A (fasting), 29 μ g. per 100 ml.; carotene, 11 μ g. per 100 ml.; fecal fat, 37 to 41 per cent of dry fecal weight. There was radiologic evidence of osteoporosis as well as dilatation and segmentation of the small intestine. The patient was given repeated transfusions and calcium salts to control the tetany.

On December 28, 1951 injections of ACTH were started. The initial daily dose was 80 mg., reduced later to 60 mg. daily. There was a temporary improvement manifested by increase in appetite, sense of well being and subsidence of diarrhea and incontinence. The serum albumin rose to 3.8 gm. per 100 ml. while the serum globulin remained at 2.8 gm. per 100 ml. Fasting serum vitamin A level rose to 82 and serum carotene to 24 μ g. per 100 ml. The improvement was transient however. The decubitus ulcer spread rapidly. The prothrombin time rose to 180 seconds. The patient developed uncontrollable tetany and died in coma on February 20, 1952. Autopsy permission was not obtained.

The fourth patient was a 67-year old man, admitted on February 28, 1956 with exacerbation of symptoms of sprue. The diagnosis was established eight years earlier and partial control was achieved with standard diet supplemented at times with liver extract, folic acid and vitamin B₁₂. During the two months prior to admission to the hospital there was an increase in number of stools to five or six daily with a weight loss of 12 pounds, reaching a low weight of 109 pounds. There was marked emaciation and clubbing of the fingers. There was also moderate edema of both ankles. The significant laboratory data were: hemoglobin, 13.9 gm. per 100 ml.; WBC, 8200 per cu. mm.; serum albumin 3.3 gm. per 100 ml.; serum globulin, 2.1 gm. per 100 ml.; glucose, 75 mg. per 100 ml.; fasting vitamin A level, 31 μ g. per 100 ml.; carotene, 6 μ g. per 100 ml.; fecal fat, 66.4 per cent of dry fecal weight with 40 per cent fatty acids; serum sodium, 142 mEq. per liter; serum potassium, 4.7 mEq. per liter; serum chloride, 107 mEq. per liter; serum calcium, 8.4 mg. per 100 ml.; serum phosphorus, 2.2 mg. per 100 ml. The patient improved on bed rest and a high protein diet supplemented with vitamins. No steroids were deemed necessary. The patient was discharged on March 25, 1955. At home there was a gradual recurrence of diarrhea and progressive weight loss. The number of stools increased to six per day. When he returned to the hospital on August 2, 1955 he appeared markedly cachectic and his weight had decreased to 72 pounds. There was marked clubbing and some edema of the legs. The blood pressure was 80/50. Laboratory findings included: hemoglobin, 11.8 gm. per 100 ml.; white blood cells, 10,000 per cu. mm.; platelets, 102,000 per cu. mm.; prothrombin time, 17 seconds (control 12 seconds); serum sodium, 148 mEq. per liter; serum potassium, 1.8 mEq. per liter; serum chloride, 115 mEq. per liter; serum calcium, 6.8 mg. per 100 ml.; serum phosphorus, 3 mg. per 100 ml. The patient appeared to be moribund. Intravenous ACTH was started together with intravenous administration of serum albumin. Patient expired the next day. Autopsy findings are described elsewhere in this symposium (Ref. 29, Case 10).

PRECAUTIONS IN LONG TERM STEROID THERAPY

It is generally known that the use of these potent hormones is associated with certain hazards such as, thromboembolic phenomena, changes in cardiovascular dynamics, ulcerations with bleeding or perforations of the gastrointestinal tract. In this group of patients complications attributable to steroid therapy have not been frequent. This is probably due to the low doses used during the long term management. Typical moon face or other changes included in the so-called Cushing's syndrome were not observed. Alterations of serum lipids have not been observed. Similarly, only minor cardiovascular changes were observed attributable to salt and water retention.

We have seen, at times, symptoms suggestive of peptic ulcer; but we have never been able to demonstrate a definite peptic ulcer attributable to the prolonged steroid therapy. Systematic administration of antacids in these instances is advisable. An unusual type of ulceration of the small bowel was described above (Case 3, Table III).

Another major problem during long term management with steroids is the possibility of masked infections. We have seen extensive pneumonitis without the usual fever and leukocytosis. Our follow-up routine includes yearly chest films. To date we have not observed reactivation of tuberculosis. Other authors have reported such instances (17). When fractures were observed during steroid therapy it was impossible to determine the part attributable to the basic malabsorption of calcium and vitamin D and the negative balance due to steroid therapy. A detailed discussion of this subject will be found elsewhere in this symposium (25). Similarly the degenerative neurologic manifestations seen in three cases could not be attributed specifically to the steroid therapy (30). There is a report of a psychosis observed in a patient with sprue during administration of large doses of cortisone at the beginning of the treatment, but not with the lower doses used later for maintenance purposes (31).

SUMMARY AND CONCLUSIONS

The management of the malabsorption syndrome has been reviewed. Dietary management, both the so-called conventional diet and gluten-free diet, have been discussed. The milder forms of this syndrome are treated with diet alone or with supplements of liver extract, vitamin B complex, vitamin B₁₂, folic acid and iron. Other vitamins and minerals may be required.

Patients resistant to the above measure can benefit by the use of corticotropin or the cortisones. There is now abundant evidence that prolonged steroid therapy is relatively safe and effective. The possible hazards of this form of therapy must be kept in mind in order to institute preventive and curative measures. Prevention and treatment of complications of steroid therapy have been discussed.

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MALABSORPTION FOLLOWING EXTENSIVE SMALL INTESTINAL RESECTION INCLUDING INADVERTENT GASTRO-ILEOSTOMY

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Extensive resection of the small intestine may be necessitated by: (a) diffuse inflammatory disease such as tuberculous enteritis or non-specific granulomatous jejuno-ileitis, (b) neoplastic disease of the small bowel, (c) mesenteric venous or arterial thrombosis, or (d) mechanical obstruction of the bowel with compromise of the blood supply as seen in volvulus or intussusception. The outcome following massive resection depends upon a number of factors, the most important of which are the general condition of the patient before resection, the length of remaining intestine and its ability to develop compensatory mechanisms.

The effects of removal of considerable portions of the small gut have been studied in great detail in the experimental animal (1). In most instances the following sequence of events was observed. Initially, steatorrhea and marked loss of weight ensued. Fat and nitrogen losses in the stool often amounted to three-quarters of the intake, whereas carbohydrates were more adequately absorbed. Fat absorption was usually improved by decreasing the amount of fat in the diet. A marked compensatory hypertrophy of the intestinal villi occurred in all animals except those with the most extensive resections and was instrumental in initiating the recovery phase which generally began four to five months after resection. Removal of more than 70 to 80 per cent of the small intestine usually resulted in death due to gradual inanition. In general, 50 per cent removal constituted the upper limit of safety in experimental enterectomy.

We have had the opportunity to observe 11 patients who have had extensive resection of the small bowel; five for jejuno-ileitis and six for acute conditions which caused gangrene of the bowel. Of the latter, resection was performed for mesenteric venous occlusion in two patients and in one patient each for superior mesenteric arterial occlusion, gangrene of the small bowel secondary to herniation of bowel through an incisional hernia, necrosis of ileum and jejunum associated with prolonged Miller-Abbott tube intubation, and volvulus of the small bowel occurring as a post-operative complication of ileo-colectomy for carcinoma of the ascending colon. The last patient succumbed after a seven month post-operative period, the only fatality in the series. The remaining ten cases have been followed for periods ranging from one to twelve years. We are reporting an additional case in which gastro-ileostomy was performed inadvertently in the course of a gastrectomy for duodenal ulcer. Because of the exclusion of a

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considerable segment of the bowel a nutritional defect resulted simulating the clinical picture observed after massive resection of the gut.

Five case histories have been selected in order to illustrate in detail the problems involved. Three patients had small intestinal resections for jejuno-ileitis and two for acute vascular accidents. These and the remaining cases have been summarized in Tables I through V.

ILLUSTRATIVE CASES

Case 1

S. K., a 43 year old white male, had an appendectomy at the age of 16 years because of intermittent episodes of right lower quadrant pain of three years duration. Several days after the operation, a right lower quadrant fistula developed which drained liquid feces. He was admitted to The Mount Sinai Hospital in 1932 where an ileo-transverse colostomy was performed with exclusion of the fistula which emanated from a granulomatous cecal mass. Six months later, he was readmitted with severe, cramping left lower quadrant pain. At operation, 12 inches of granulomatous terminal ileum were resected. He remained essentially asymptomatic for 20 years.

Early in 1952 abdominal cramps, anorexia, weight loss, mild fever, diarrhea and severe fatigue appeared. Roentgen examination showed extensive disease proximal to the anastomosis. The distal jejunum as well as the remainder of the ileum were involved. In April of that year he was readmitted and at operation the disease was found to be so extensive as to require massive resection of the small and large bowel starting 18 inches below the ligament of Treitz and extending to the distal transverse colon, and jejunio-transverse colostomy. His postoperative course was uneventful except for eight to ten loose stools daily. A low residue diet, deodorized tincture of opium, bismuth subcarbonate, folic acid, vitamins and injections of crude liver extract failed to alleviate the diarrhea. Laboratory studies revealed evidence of malabsorption. An oral glucose tolerance as well as a vitamin A tolerance test showed completely flat curves (Table V). The serum carotene concentration was strikingly low (8 μ g. per cent).

In August 1952, he was started on a course of ACTH, 80 units daily by intravenous drip. The improvement was striking. Appetite and strength improved and he gained seven pounds in two weeks. The dosage of ACTH was gradually reduced to 20 units daily and on discharge it was replaced by cortisone, 75 mg. daily, without deleterious effect. In October 1952, while the patient continued with a daily maintenance dose of 25 mg. of cortisone, signs of disordered sensorium appeared and steroids were discontinued in order to prevent a psychosis. His weight, which had fallen some 59 pounds, was now stabilized at 125 pounds. When cortisone was discontinued, he began to note twitching of his facial muscles, tingling sensations and cramps in his legs. He was readmitted to the hospital in November, 1952 for reevaluation of these symptoms. The Chvostek and Trousseau signs were positive. Chemical analyses of blood drawn the day after admission were: serum calcium, 6.4 mg. per cent; phosphorus, 2.8 mg. per cent; alkaline phosphatase, 9 King Armstrong units; total protein, 6.4 mg. per cent; albumin 2.5 and globulin 3.9 gm. per cent; and total cholesterol, 120 mg. per cent. The esterified cholesterol was 75 per cent of the total. The fecal fat amounted to 55.8 per cent of the dry stool weight, 41.7 per cent comprising the fatty acid portion. Vitamin A tolerance test revealed improved absorption of fat-soluble vitamins although the level of carotene in the serum was still extremely low. Glucose tolerance test showed somewhat improved absorption, although the curve was not completely normal. Gastric analysis after administration of histamine showed absence of hydrochloric acid. Urinalysis was positive for albumin. There was fixation of the specific gravity at 1.010 and reduction in the excretion of phenolsulphthalein to 42 per cent. Electrolyte and renal clearance studies were interpreted as compatible with the diagnosis of renal tubular acid-

osis. This was perhaps related to repeated episodes of dehydration, loss of potassium and subsequent renal ischemia producing chronic renal insufficiency.

Roentgen examination revealed normal residual small bowel; barium was seen in the colon after 15 minutes. There was a moderate degree of demineralization of the bones.

Several days after admission, he had a tetanic convulsion which responded to intravenous calcium gluconate. He was placed on high doses of calcium lactate and vitamin D by mouth. This resulted in a complete cessation of muscular twitching. Although diarrhea persisted (average of seven evacuations daily) he was discharged markedly improved on a high calorie, high protein, high carbohydrate, low residue diet with liberal amounts of salt and potassium chloride. Vitamin D and calcium lactate were continued in high doses.

He remained well until August 1953 when a non specific febrile illness again precipitated acidosis, cramps, vomiting, dehydration and postural hypotension. Chemical analysis revealed severe electrolyte imbalance as evidenced by: the CO_2 combining power of 13.6 vol. per cent and the sodium 125 mEq./L. After therapy with parenteral fluids and electrolytes, he became afebrile, the abdominal cramps subsided and his appetite improved. Repeated serum electrolyte studies showed the CO_2 combining power to be 69 vol. per cent, and the sodium to be 144 mEq./L., and the chloride to be 114 mEq./L. The diarrhea persisted with six to ten stools daily. Small bowel study again revealed a normal jejunum. Thirty minutes after ingestion of barium, the head of the column was seen in the rectum.

The patient's condition remained good until January 1954, when he was admitted because of rectal bleeding thought to be caused by recurrent jejunitis. X-ray examination failed to confirm this assumption. After control of the bleeding by conservative measures, he remained well until the latter part of 1954 when rectal bleeding recurred. The hemoglobin on admission was 6.8 gm. per cent, the prothrombin time was 18.5 sec. (control 11 sec.), serum albumin was 2.0 gm. per cent, and serum globulin was 3.3 gm. per cent. The bleeding promptly ceased after administration of vitamin K and the prothrombin time returned to normal. He was given fluids, electrolytes, one blood transfusion, and then oral iron therapy was begun. Anoscopic examination revealed an anal fissure posteriorly and external hemorrhoids. He later developed a perirectal abscess which required incision and drainage.

In 1955, he remained comparatively well. There were intermittent episodes of mild abdominal cramps and four to seven soft but formed bowel movements per day. Careful selection of diet and multivitamin preparations constituted his therapy. Calcium salts and all forms of iron produced severe abdominal cramps and were withheld. During a two month period of steroid therapy (10 mg. of hydrocortisone by mouth daily) he gained ten pounds but once again, the development of mental confusion required the discontinuance of this medication. In January, 1956 he was hospitalized for progressive swelling of the buttocks and pruritus. On physical examination, he showed areas of excoriation especially marked over the buttocks with the skin over the perineum showing a red macular eruption. There was an abscess present between the fourth and fifth toes of the right foot.

Urine analysis revealed 1+ albumin, but was otherwise negative. Hemoglobin was 8.7 gm. per cent. The red cells were hypochromic. Abnormal blood findings included: serum alkaline phosphatase, 19 King Armstrong units; total protein, 5.7 gm. per cent, albumin, 2.0 and globulin, 3.7 gm. per cent. Oral glucose tolerance test revealed a flat curve. A vitamin A tolerance test showed a low fasting level and delayed absorption. The serum carotene level was extremely low (3 μg . per cent).

The secretin test (performed by Dr. David Dreiling) revealed normal volume with low bicarbonate concentration and low concentration of amylase, indicating pancreatic insufficiency as seen in pancreatic fibrosis (see Table IV). Gastric analysis revealed a histamine-resistant achlorhydria. The stools contained large amounts of fatty acids and considerable neutral fat. The Schilling test demonstrated complete lack of vitamin B_{12} absorption. Roentgen studies of the remaining small bowel were again negative.

He was treated with salt-free albumin and blood, which raised his serum albumin level to 3.3 gm. per cent. The abscess healed readily with the use of antibiotics. He was given 9 grams of pancreatin daily but this proved ineffective in controlling the diarrhea and

steatorrhea. Because of previous episodes of mental confusion during treatment with the steroid hormones there was some hesitancy to administer these agents. A cautious trial with prednisone had very gratifying results, and he has been maintained on 20 mg. of prednisone daily to the time of this writing (Oct. 1956). His weight is now 140 pounds, appetite is satisfactory and the pruritus is under control. He has five formed stools daily. His diet consists of 350 grams of carbohydrate, 100 grams of protein and 60 grams of fat. In addition to prednisone and a weekly injection of corticotropin, he also receives potassium chloride, vitamin D, calcium lactate and testosterone.

The most recent roentgen study of the gastrointestinal tract revealed the jejunum to be longer than 18 inches, perhaps a compensatory hypertrophy.

It is of interest that among the close blood relatives of this patient there is a high incidence of jejuno-ileitis and colitis (Fig. 1).

Comment. This patient's symptoms began in 1929 at the age of 13 years. Three years later an appendectomy was performed for "chronic appendicitis". Because of a fistulous tract extending to and from a mass in the pericecal region an ileo-transverse colostomy with exclusion of the mass was performed several months later. After resection of one foot of granulomatous ileum in 1932 a remission of almost 20 years resulted. In 1952 when disease recurred, all of the involved small bowel was eradicated by extensive resection and only 18 inches of proximal jejunum were left. The postoperative course was complicated by almost continuous diarrhea, vomiting, anorexia, intercurrent infections, dehydration, cachexia, tetany, and renal involvement which suggested tubular acidosis. There was severe impairment of intestinal absorption in the immediate postoperative period, with flat glucose tolerance and flat vitamin A tolerance curves. Six months later there was improvement in the absorptive capacity of the bowel

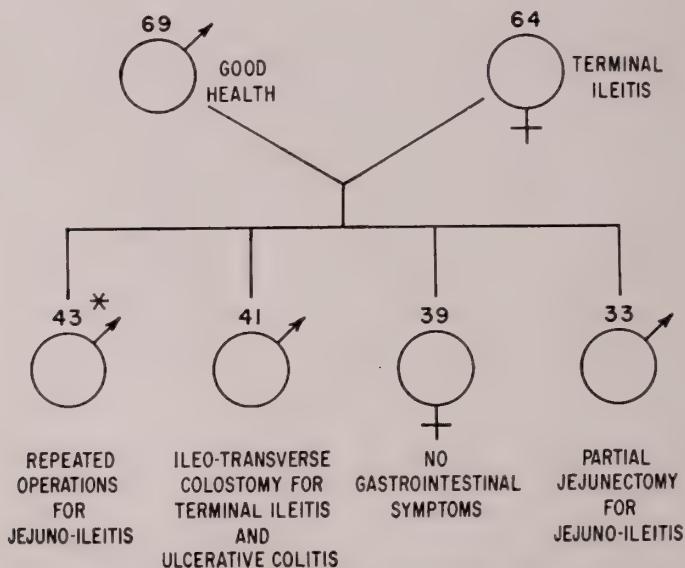


FIG. 1. Family tree of patient 1. Asterisk indicates the index patient (proband). His mother and one brother had jejuno-ileitis; another brother had terminal ileitis and ulcerative colitis; a sister had no gastrointestinal disease.

It is noteworthy that the patient received steroid therapy during this six month interval. Bleeding episodes in 1954 may have been due to hypoprothrombinemia and inflammation at the anastomotic site, but there was no evidence that disease had recurred in the remaining jejunum. Recently, treatment with prednisone and ACTH has resulted in marked improvement in his general condition.

Case 2

D. H. is a 58 year old white female who, because of abdominal pain, had an exploratory laparotomy performed in 1945 at another hospital. The diagnosis of jejuno ileitis was established but no definitive procedure was done because the disease was considered too diffuse. In May 1950 severe abdominal pain recurred and she lost considerable weight. Two months later, during her first admission to The Mount Sinai Hospital (July 1950), it was decided to treat the disease surgically. At operation all of the small bowel except for six feet of proximal jejunum was found involved in the disease process. A jejunio transverse colostomy was constructed about five feet from the ligament of Treitz, by passing all of the diseased bowel. The postoperative course was uneventful except for four semi formed bowel movements per day. Her condition continued to improve over a six month period but in December 1950 she again began to lose weight and had recurrent abdominal cramps. She was readmitted to the hospital where the short-circuited intestine together with the cecum was resected and a new jejunio-transverse colostomy performed. She was left with approximately three feet of small bowel. In the first six months after operation, she had two to four semi-formed evacuations daily and her condition improved markedly.

In May 1951 the patient began to have four to five diarrheal stools daily, following the ingestion of foods or liquids. She restricted her diet and soon showed evidences of malnutrition and dehydration. When readmitted to the hospital, she was given frequent feedings, a diet high in vitamins, tincture of opium, Kaopectate and sedation. The diarrhea subsided and she gained six pounds in one week. Shortly after discharge she again developed diarrhea. Examination of the stool revealed a large amount of fatty acids and neutral fats. On the assumption that increasing the length of functioning colon would increase the absorption of water and solidify the stools, it was decided to convert the jejunio-transverse colostomy to a jejunio-ascending colostomy, thus adding 12 inches to the functioning colon. The results were indeed gratifying, as the diarrhea subsided after operation. She was well until November 1952 when anemia was noted for the first time, and she was hospitalized for investigation of this problem. Hematologic studies revealed the following: hemoglobin, 6.6 gm. per cent; red blood count, 2.9 million per cu. mm.; hematocrit, 29 per cent; white blood count and differential counts were normal. The blood smear showed an absence of macrocytes; the red cells, generally well filled with hemoglobin, were small and uniform in size and shape. A bone marrow puncture showed mild granulocytic hyperplasia, but was not diagnostic. Serum iron was 51 μ g. per cent and total iron binding capacity 363 μ g. per cent. The platelets were adequate in number and morphologically normal. The Coombs' test was negative as were the stool guaiac examinations. The anemia was thought to be due to poor iron absorption. After six blood transfusions her hemoglobin was 13.8 gm. per cent. She was discharged on a high calorie, low residue diet with supplemental feedings, multivitamins, ferrous sulfate and sedation.

In April, 1953 she complained of rectal discomfort. Examination revealed extensive internal and external hemorrhoids for which hemorrhoidectomy was performed uneventfully. In May, 1953 the patient fell on her right side. This resulted in severe pain in the region of the right hip with loss of function of that joint. Roentgen examination revealed a chip fracture and also marked osteoporosis of the skeletal system. Pain and disability persisted for many months until traction was applied.

In December 1953, the patient was hospitalized because of severe posterior neck pain which had existed for several months. Roentgen studies showed narrowing of the interspaces

between cervical vertebrae 4-5 and 5-6. Treatment with hormones was instituted for osteoporosis. In 1954 she was comparatively well, although recurrent anemia necessitated transfusions and admission to the hospital on several occasions. In January 1955, she was hospitalized because of weakness and recurrence of diarrhea. The abdomen was soft and a non-tender liver was palpated one and a half fingers beneath the costal margin. The hemoglobin was 10.2 gm. per cent. The red blood count was 3.85 million per cu. mm. The reticulocyte count was 3.8 per cent. Chemical analyses of the blood revealed the following: serum bilirubin, 0.17 mg. per cent; alkaline phosphatase, 16.7 King Armstrong units; total protein, 6.2 gm. per cent with albumin 2.9 and globulin 3.3 gm. per cent. The calcium level was 7.5 mg. per cent and the phosphorus, 2.5 mg. per cent. Barium meal examination showed the stomach, duodenum and residual jejunum to be normal. The transit time was rapid; the cecum filled with barium in 30 minutes. The skeletal system showed marked generalized demineralization. The patient was treated with Kaopectate and deodorized tincture of opium and the diarrhea rapidly subsided. She was discharged on high doses of calcium lactate, calciferol and testosterone.

In August 1955 she was admitted because of crampy right lower quadrant pain and diarrhea. Physical examination revealed a dry and fissured tongue. The abdomen was slightly distended and active bowel sounds were present. The liver was enlarged two fingers below the costal margin and was non-tender. No other organs or masses were palpable. Liver function tests were negative. Recurrent disease of the small bowel was suspected, but x-ray study did not confirm this impression. The diarrhea was controlled with the usual anti-diarrheal agents and the general condition rapidly improved. She was discharged on a high protein diet, vitamin B₁₂, testosterone, ferrous sulfate and multivitamins.

Recurrent severe anemia has necessitated readmission to the hospital on three occasions for which she received multiple blood transfusions. When last seen (September 1956), she weighed 92 pounds, 12 pounds more than her preoperative weight, her appetite was good and she was having three or four semi-formed bowel movements daily. Therapy included oral ferrous sulfate, calcium lactate, testosterone and vitamin B₁₂.

Comment: The diagnosis of jejuno-ileitis was established in 1945. Five years later a jejuno-transverse colostomy was done excluding all but six feet of proximal jejunum. She remained well for six months but then symptoms recurred, requiring resection of the by-passed intestine and cecum and establishment of a jejuno-transverse colostomy. Approximately three feet of proximal jejunum were left behind. Six months after resection, because of diarrhea and inability to gain weight, the jejuno-transverse colostomy was converted into a jejuno-ascending colostomy in order to increase the length of functioning colon, perhaps thereby increasing the absorption of water and electrolytes. The operation was helpful; her stools became solidified and she gained weight. Her chief remaining problem has been severe anemia, probably due to poor iron absorption which has required frequent transfusions. An additional difficulty has been osteomalacia, manifested by pseudo-fractures, collapsed vertebrae and diffuse demineralization of the entire skeletal system. Although she weighs only 92 pounds, this is 12 pounds more than her preoperative weight. She is not troubled by diarrhea, having three or four semi-formed bowel movements per day.

Case 3

I. R., A 30 year old white male, was admitted to The Mount Sinai Hospital in September 1955, complaining of diarrhea of four weeks duration. His illness began in 1945 with episodes of severe crampy abdominal pain usually associated with vomiting. In 1947 diarrhea was

accompanied by abdominal cramps and he suffered a 20 pound weight loss. From 1945 to 1949 he had four upper gastrointestinal roentgen examinations and two barium enema studies with no abnormalities noted. In February 1949, a small bowel study revealed a markedly dilated loop of jejunum and he was hospitalized in March 1949, with the diagnosis of regional enteritis. Laboratory data showed a hemoglobin of 13.2 gm. per cent and a serum albumin concentration of 4.2 gm. per cent and globulin of 3.4 gm. per cent.

Exploratory laparotomy in March 1949 revealed seven areas of segmental enteritis involving the proximal jejunum, starting about 20 cm. distal to the ligament of Treitz and extending over seven feet of jejunum with skip areas of normal jejunum between the lesions. The mesentery of the involved jejunum was markedly edematous and thickened with enlarged lymph nodes. Large inflammatory nodes were present over the pancreas. The remainder of the gastrointestinal tract appeared normal. The bowel proximal to the involved jejunum was dilated and hypertrophied to a moderate degree. Since the involvement was localized to seven feet of bowel, a resection of the involved bowel with a side-to-side anastomosis was performed.

Following operation, the patient showed marked improvement and gained 60 pounds in six months. He remained well for a period of three years when he again developed voluminous diarrhea of foul smelling stools. Abdominal cramps occurred much more frequently than they did prior to resection. In 1951 treatment with broad spectrum antibiotics was ineffectual. In 1952 cortisone therapy resulted in no improvement. In 1953 and again in February 1955 he had episodes of tarry stools and required blood transfusions. Laboratory data prior to transfusions in March 1953 revealed a hemoglobin of 4.3 gm. per cent; RBC, 1.7 million per cu. mm., serum calcium, 8.2 mg. per cent, albumin, 2.2 gm. per cent and globulin, 1.7 gm. per cent. His disease was marked by periods of remissions and exacerbations. He had frequent attacks of paresthesias followed by carpal spasms suggestive of tetany. He noted bright red blood in the stools and edema of the ankles following very severe bouts of diarrhea.

In August 1955 he had a recurrence of diarrhea, mild abdominal cramps and weakness. Four weeks of bed rest, low residue diet and anti-diarrheal agents failed to check the symptoms and he was admitted to the hospital September 1955.

Physical examination revealed an emaciated young man, chronically ill, weighing 109 pounds. Temperature was 101°F., pulse rate 116 per minute, blood pressure 115/60. He was moderately dehydrated and severely anemic. The abdomen was moderately distended. No viscera or masses were palpable. Rectal examination was negative except for hemorrhoids. The stool was tan, liquid and guaiac-positive. Lymph nodes were present bilaterally in the inguinal region and in the right axilla. The Chvostek and Trousseau signs were positive.

Laboratory data: Hemoglobin, 6.1 gm. per cent; WBC, 5000 per cu. mm., with a normal differential count; ESR, 61 mm. (Westergren). Chemical analysis of the serum: blood urea nitrogen, 10 mg. per cent; fasting blood sugar, 97 mg. per cent; albumin, 2.8 and globulin, 2.2 gm. per cent; calcium, 8.2 mg. per cent; phosphorus, 3.2 mg. per cent; alkaline phosphatase, 9.0 King Armstrong units; serum iron, 33 μ g. per cent; total iron binding capacity, 250 μ g. per cent. Oral glucose and vitamin A tolerance tests were flat and the secretin test of pancreatic function was abnormal. The fat content of the feces was 56.4 per cent of the dry fecal weight, fatty acids accounting for 20.8 per cent of the total.

Barium enema examination revealed marked dilatation and redundancy of the colon. There was no delay or obstruction to the retrograde flow of barium. An upper gastrointestinal and small bowel examination was reported as follows: There were no abnormalities in the stomach or duodenum. Some of the barium left the stomach promptly and visualized the proximal loops of jejunum. The mucosal pattern of the most distal portion of the duodenum and the adjacent portion of the jejunum was thickened and somewhat irregular but this region appeared to be normally distensible. However, beginning four or five inches from the ligament of Treitz the outlined loops of jejunum were markedly irregular in configuration, contained secretions, and the mucosal pattern was markedly effaced. In this region there appeared to be an area of saccular dilatation about 2½ inches in diameter which

retained barium. Loops of jejunum distal to this saccular dilatation occupied the left side of the abdomen and the left iliac fossa and showed a marked irregularity and coarse nodular thickening of the mucosal pattern. These loops never filled well with barium nor were any loops distal to these on the right side of the abdomen well visualized at any time. Barium was seen in the ascending colon about three hours after the administration of barium by mouth, but the region of the ileocecal valve could not be identified. The colon was markedly distended with air throughout its course. About ten hours after the administration of barium the dilated saccular structure described above was located in the mid-line and a small amount of barium was seen in the descending colon and sigmoid. Twenty-four hours after the administration of barium, there was no evidence of retention in the saccular structure. A loop of bowel on the right side of the pelvis was seen at this time and also showed a markedly nodular irregular mucosal pattern. This did not appear to be dilated. The findings described were indicative of inflammatory disease of practically all of the small bowel. The most severe disease appeared to be a short distance from the ligament of Treitz on the left side of the abdomen. There was a strong possibility that multiple fistulas existed in this area.

The patient was treated with intravenous serum albumin, parenteral calcium gluconate, multivitamins, Kaopectate and sedation, in addition to receiving three blood transfusions which brought his hemoglobin up to 11.4 gm. per cent. After ten days his condition was only slightly improved and therapy with ACTH, 40 units daily intramuscularly, was started. Four days later, he had a massive rectal hemorrhage requiring five blood transfusions. The corticotropin therapy was discontinued but he had three more massive rectal hemorrhages during the next seven days. Each episode was accompanied by colicky abdominal pain requiring parenteral codeine. Numerous transfusions were required to replace the blood loss. Conservative therapy was continued and one week after the fourth hemorrhage the stools were negative for occult blood. After the bleeding ceased, his appetite improved and he gained six pounds in two weeks. His strength increased and his general condition improved sufficiently to warrant discharge to a convalescent home 12 days after his stool contained no occult blood.

Comment: This patient's disease was originally confined to seven feet of proximal jejunum, and the improvement in his condition after resection of the diseased tissue was indeed dramatic. Three years after operation, he had a recurrence of jejunitis which soon developed into jejuno-ileitis and resulted in a 65 pound weight loss. X-rays four years after recurrence, showed diffuse involvement of the entire remaining small bowel with multiple fistulas present. Profound disturbances in intestinal absorption resulted, as evidenced by tetany, edema, flat glucose and vitamin A tolerance tests, abnormal secretin test, and a high percentage of fat in the stools. An additional complication was recurrent massive hemorrhage from the bowel, not commonly seen in jejuno-ileitis, which was a distinct threat to the life of this patient.

Resection of seven feet of small intestine is considered "massive", but resection of this magnitude is not necessarily accompanied by serious sequelae. However, when the balance of the small intestine became involved in the inflammatory process, the full-blown malabsorption syndrome ensued.

Case 6

E. G. was a 53 year old female who in 1938 had a combined abdomino-perineal resection for carcinoma of the rectum with a permanent sigmoid colostomy. In 1947, a laparotomy was performed because of the sudden onset of bloody diarrhea. There was no evidence of

recurrence of the malignancy and the etiology of the acute diarrhea was not determined. In August 1948, she was admitted to the Syracuse University Hospital in profound shock. Laparotomy revealed gangrenous bowel in a large ventral hernial sac at the site of the previous laparotomy. Torsion of the mesentery had occurred and the entire small intestine was gangrenous from a point 18 inches distal to the ligament of Treitz to the cecum. Seven feet of small intestine were resected. The patient survived the procedure but developed constant severe diarrhea from the colostomy. Drugs to thicken the stool, including deodorized tincture of opium, paregoric, bismuth and atropine were unsuccessful in controlling the diarrhea. When she began oral feedings, they were provided as easily assimilated foods such as glucose and protein hydrolysates fortified with vitamins in adequate doses. She tolerated small volumes of foods at frequent intervals, but large meals caused dyspepsia. After returning home, she averaged six to eight small feedings a day with supplements of glucose, milk, proteins, vitamins and calcium. Fats were poorly tolerated and were reduced to a minimum. She consumed 2000 to 2500 calories a day. A gastrointestinal series performed several months after discharge revealed a very small residual segment of small intestine, 18 inches in length, with only moderate dilatation of this loop. Sharp weight loss and progressive cachexia were anticipated but the patient did not deteriorate seriously. Her weight slowly fell from the preoperative level of 120 pounds to 100 pounds. The chief cause of her disability rested with the almost continuous discharge from the colostomy. The skin and muscle turgor remained good, and she never demonstrated evidences of gross vitamin deficiency. Blood studies at monthly intervals showed normal blood counts and blood protein levels. Although she was unable to do a full day's work, she was capable of light household duties.

In an effort to explain the maintenance of an adequate nutritional state in the face of gross intestinal deficiency, the patient was admitted to University Hospital in Syracuse, New York in January 1949, where special studies on absorption and excretion of nitrogen and fat were done (2). They demonstrated that the patient was unable to absorb much fat, but partition studies showed that fat hydrolysis was carried on in normal fashion. Fats in the stools amounted to 42.8 per cent of the dry weight while the fatty acid fraction was 31.2 per cent. Soaps and neutral fats were excreted in normal quantities. Nitrogen balance studies indicated that she absorbed only slightly more than half of the nitrogen ingested, but this was enough to maintain a positive balance. An oral glucose tolerance test was normal.

In March 1950, she was admitted to The Mount Sinai Hospital for further metabolic studies and treatment of the diarrhea. Physical examination revealed a poorly nourished female weighing 85 pounds. The positive physical findings were limited to the following: the tongue was smooth, somewhat shiny and red; a patent colostomy was seen with no induration or skin irritation in the region of the stoma; 2 plus pitting ankle edema, and clubbing of the fingers.

Hematologic determinations and chemical analysis of the serum was within normal limits except for a slight elevation in the alkaline phosphatase. Oral glucose and vitamin A tolerance tests were normal, although the fasting level of vitamin A in the serum was low. The serum carotene concentration was very low. Two days later Tween 80 was added to the oily suspension of vitamin A. The test was repeated and showed some improvement of vitamin A absorption (Table V).

She was placed on a high protein diet with frequent feedings of bananas and strawberries between meals. She was given 15 μ g. of vitamin B₁₂ parenterally for one week, along with deodorized tincture of opium. These measures did not control the diarrhea. She was then given calcium carbonate to decrease the acidity of the intestinal contents because of the possibility that the low pH of the intestinal contents might have been a factor in producing the hypermotility. Coincident with the administration of calcium carbonate, the patient's stools became formed. She gained five pounds, and her general well being improved remarkably. Roentgen studies with the administration of calcium carbonate showed a distinct decrease in the passage time through the small intestine. When a barium meal was given

without the calcium, the small bowel was visualized for one hour and barium appeared at the colostomy site at the end of this time. Several days later when calcium carbonate was administered with the barium meal, the small bowel remained visualized for over three hours and barium did not appear at the colostomy site until three and one-half hours after the meal. One week prior to discharge the opium was discontinued and only calcium carbonate was administered. The diarrhea recurred indicating the need for both the deodorized tincture of opium and the calcium carbonate. She was discharged on these agents in addition to a low residue, high carbohydrate, high protein, low fat diet, with vitamin supplement.

After her return to Syracuse, she was seen at frequent intervals by Drs. Berman and Haft for one year but then was lost to follow-up. During that year she was able to indulge in non-strenuous activities. She suffered frequent bouts of diarrhea but maintained her weight between 90 and 95 pounds.

Comment. Nine years after an abdomino-perineal resection for carcinoma of the rectum, which resulted in a permanent sigmoid colostomy, this patient had seven feet of gangrenous small bowel resected because of ventral herniation of the bowel through an incisional hernia. She recovered from the operation which left her with only 18 inches of proximal small bowel. Her nutritional status remained remarkably good despite voluminous discharges from her colostomy. Studies indicated good carbohydrate absorption, positive nitrogen balance, but excessive fat loss in the stools. Study of lipid absorption by the vitamin A test three months later indicated improved fat absorption. The ability of the intestine to absorb glucose and protein improved more readily than fat. The improvement in fat absorption noted so soon after resection was a good prognostic sign.

Case 7

A. S., a 66 year old white female, was admitted to The Mount Sinai Hospital in November 1954, for treatment of long standing hyperthyroidism. Administration of radioactive iodine was successful in amelioration of the symptoms except for chronic auricular fibrillation which persisted.

In May 1955, she was readmitted for conversion of arrhythmia. She was treated with digitalis and then with quinidine, with conversion to regular sinus rhythm. She was discharged in good condition. As she was leaving the hospital, she developed severe abdominal pain and was readmitted. Emergency surgery was deemed necessary. Exploratory laparotomy revealed extensive small bowel infarction secondary to embolization of the superior mesenteric artery. The small bowel, except for 18 inches of jejunum, was resected as well as the right side of the colon and the proximal half of the transverse colon. The postoperative course was complicated by acute cholecystitis with jaundice requiring cholecystectomy on the eighth postoperative day. Following the bowel surgery, she had five to ten diarrheal stools per day and her weight decreased from 119 to 96 pounds. She stabilized sufficiently on vitamins and Kaopectate to allow discharge.

She was readmitted in August 1955 because of recurrence of diarrhea and muscular twitchings suggestive of hypocalcemia. Malabsorption was evident on this admission. Laboratory studies revealed the following: hemoglobin, 10 gm. per cent, calcium, 7.8 mg. per cent; total protein, 7.4 gm. per cent; albumin, 3 gm. per cent; and globulin, 4.4 gm. per cent. The prothrombin time was 14.5 seconds (control, 12 seconds). An oral glucose tolerance test and a vitamin A tolerance test showed markedly impaired absorption of carbohydrate and fat and there was no absorption of vitamin B₁₂ as measured by the Schilling test. Roentgen examination of the residual small bowel and colon was negative except for rapid transit time; barium appeared in the colon in 15 minutes. Stool examinations were negative for occult blood and neutral fat, but fatty acids were present in abundance. Gastric analysis showed normal acidity.

The diarrhea persisted despite Kaopectate, deodorized tincture of opium, calcium chloride and a high calorie, low fat diet. It was not until cortisone, 100 mg. daily, was added to the regimen that her condition improved. She gained five pounds in two weeks and her evacuations were limited to two semi formed stools per day. She was discharged in October 1955 on prednisone, 30 mg. per day. Supportive therapy included vitamins and Kaopectate.

When last seen in March 1956, her general condition was good, although she weighed only 102 pounds. She had three to four bowel movements per day which were semi formed, yellowish and occasionally fatty. Hematologic and serum chemistry studies were normal.

Comment. The sequence of events that created this patient's nutritional problem is of interest. In 1955, she was hospitalized for conversion of chronic auricular fibrillation. This was easily accomplished with digitalis and quinidine. She was discharged the day after conversion and as she was leaving the hospital developed acute abdominal pain. Exploratory laparotomy revealed extensive small bowel infarction secondary to an embolus from the superior mesenteric artery. After an extensive resection, she was left with approximately 18 inches of jejunum. The postoperative course was complicated by jaundice requiring cholecystectomy on the eighth day. Since then, the patient has been troubled with weight loss, diarrhea, abdominal cramping pain, tremulousness and irritability. Extensive workup three months after operation revealed flat vitamin A and glucose tolerance curves, failure to absorb vitamin B12, rapid intestinal transit time and moderate demineralization of the bones. The diarrhea was not controlled by the usual agents and her weight dropped from 98 to 84 pounds. Upon the administration of cortisone, the diarrhea rapidly abated, and she gained seven pounds in two weeks. She has been maintained on prednisone and has been doing remarkably well although confined to her home for the most part.

Case 12

L. S., a 64-year old male, was admitted to The Mount Sinai Hospital in January 1956 complaining of weakness and weight loss following subtotal gastrectomy.

The patient had no gastrointestinal complaints until two years prior to admission when he developed abdominal pains which occurred two hours after meals. A roentgen study of the upper gastrointestinal tract at that time was reported as negative. In July 1955 he had an episode of hematemesis while in Florida. He was treated with transfusions until bleeding ceased and then discharged without investigation of the source of bleeding. Upon arrival in New York City he had a recurrence of hematemesis and was hospitalized at another institution. He received eight units of blood in two days but the bleeding persisted and on the third hospital day, a subtotal gastrectomy for duodenal ulcer was performed. He was discharged on the twelfth postoperative day on a diet of milk, cereal and baby food which was gradually increased, but the patient failed to gain weight although his appetite was excellent and he was consuming three large meals daily supplemented with vitamins and iron. His weight gradually fell from the preoperative weight of 148 pounds to 108 pounds. In October 1955 he had an episode of dizziness followed by the passage of tarry stools and subsequent fainting and was readmitted to that hospital. After the bleeding was controlled, a vagotomy was suggested but refused by the patient. Shortly after discharge he noted a change in bowel habits, his movements became more frequent and soft. Because of persistent weakness and inability to gain weight he was admitted to The Mount Sinai Hospital for investigation.

Physical examination was negative except for evidence of marked weight loss. Laboratory data: hemoglobin, 10.5 gm. per cent; WBC, 6,000 with a normal differential count; erythrocyte sedimentation rate, 5 mm. per hour (Westergren method); blood urea nitrogen,

18 mg. per cent; fasting blood sugar, 83 mg. per cent; total protein, 5.0 gm. per cent; albumin, 2.6 and globulin, 2.4 gm. per cent; bromsulfalein (5 mg., 45 min. test), 1.8 per cent retention of the dye; alkaline phosphatase, 17.1 King Armstrong units; acid phosphatase, 3.8 King Armstrong units; prothrombin time, 15 seconds (control—12 seconds); cephalin flocculation, 2 plus. On gastric analysis the free hydrochloric acid was 22 mEq. per liter. Total acidity was 36 mEq. per liter. Examination of the feces for neutral fat and fatty acids was negative, as was the guaiac test for occult blood. An oral glucose tolerance test (100 gm. glucose) showed 83, 88, 97, 101 and 85 mg. per cent after 0, 30, 60, 120 and 180 minutes respectively. It was interpreted as a flat curve. A vitamin A tolerance test (180,000 u. vitamin A in oil) revealed the following vitamin A serum levels: fasting 26; after 4 hours, 44; 6 hours, 42; and 8 hours, 36 μ g. per cent. Serum carotene concentration was 18 μ g. per cent. Thus, the tests of intestinal absorption showed marked impairment of the absorptive capacity of the small bowel. A gastrointestinal series revealed that the site of the previous anastomosis was only two feet from the ileocecal valve. The stomach had been inadvertently anastomosed to the ileum.

The cause of the malabsorption was now established and the patient was again operated upon. The original anastomosis was found to be a gastroileostomy. This was resected and a gastrojejunostomy established. The postoperative course was uneventful. Within a week he was eating soft foods without difficulty and had started to gain weight. He was discharged on the eleventh postoperative day in good condition. When he was last seen, eight months after discharge, he was asymptomatic and weighed 145 pounds, only three pounds below his normal weight. The total weight gain after the operation amounted to 37 pounds.

Comment. Failure to gain weight following subtotal gastrectomy for duodenal ulcer performed six months prior to admission was the chief complaint of this patient. There was evidence of malabsorption as indicated by the glucose tolerance and vitamin A tolerance tests. Roentgen study revealed the underlying defect for the barium, administered by mouth, flowed directly from the stomach to the distal ileum. The surgical error was rectified, the postoperative course was uneventful and the patient gained 37 pounds in weight. The decisive factor causing malabsorption and the weight loss was the exclusion of all but a small segment of small bowel. The resulting malabsorption syndrome simulated massive resection of the small intestine.

CLINICAL FEATURES

Table I summarizes the clinical features of the patients. The group with jejuno-ileitis included three men and two women whose ages at the time of resection ranged from 18 to 52 years (average 38). Patient 1 had a most extensive resection; only one and one-half feet of small bowel remaining. As anticipated, this patient had an extremely stormy course after operation as did patient 2 who had all but three feet of jejunum resected. Patient 3 had six feet of jejunum resected and had a smooth postoperative course. He remained in good health for three years when disease recurred affecting almost all of the remaining small intestine. This resulted in severe impairment of absorption similar to that seen after a 90 per cent resection. Cases 4 and 5 had 50 per cent or less of the small bowel resected with no significant weight loss or nutritional deficiency. Case 6 through 11 were patients who had extensive resections for acute vascular emergencies which compromised the blood supply to the bowel. This group consisted of four females and two males ranging in age from 21 to 68 years (average 51).

TABLE I
Clinical features

Case No.	Age at Resection	Sex	Disease	Magnitude of Resection or Length of Remaining Small Intestine	Period of Observation
1. S. K.	39	M	Jejuno ileitis	1½ ft. proximal jejunum remaining	3½ yrs.
2. D. H.	52	F	Jejuno ileitis	2½ ft. proximal jejunum remaining	7 yrs.
3. L. R.	24	M	Jejuno ileitis	7 ft. proximal jejunum resected	7 yrs.
4. S. R.	41	F	Jejuno ileitis	50% of small bowel resected	11½ yrs.
5. P. G.	18	M	Jejuno ileitis	5 ft. jejunum resected	2 yrs.
6. E. G.	53	F	Herniation of bowel through hernial sac—gangrene of 17 ft. of small intestine	1½ ft. jejunum remaining	2 yrs.
7. A. S.	64	F	Superior mesenteric arterial occlusion	1½ ft. jejunum remaining	2 yrs.
8. M. S.	64	M	Necrosis of jejunum and ileum caused by indwelling Miller-Abbot tube	3 ft. jejunum remaining	8½ yrs.
9. W. B.	37	M	Mesenteric venous thrombosis	7 ft. jejunum remaining	9 yrs.
10. S. M.	21	F	Mesenteric venous thrombosis	5 ft. of small bowel resected	13½ yrs.
11. F. T.	65	M	Volvulus of the small bowel after ileo-colic resection	3 ft. jejunum resected	1 yr.

Four of them had 85 per cent or more of the bowel removed. As did the group with inflammatory disease and similarly extensive resections, these four had severe absorptive difficulties in the ensuing months and years. The patients with resection of one-third of the intestine suffered no serious sequelae from their resections.

Table II lists the signs and symptoms manifested by the patients. Diarrhea, the most common complaint, was noted in eight of eleven patients, the three patients who were not affected having had resections of small magnitude. Five patients lost from 23 to 50 pounds in the first three postoperative months. Patient 3 had a total weight loss of 65 pounds. This was not the result of resection but

TABLE II
General Characteristics—Symptoms and Signs

Case No.	Weakness	Weight Loss after Resection		Stools (Number per Day)	Vitamin B Complex Deficiency	Tetany	Edema	Abdominal Pain	Abdominal Distention
		lb.	time						
1. S. K.	+	50	3 mos.	7-8	+	+	+	+	+
2. D. H.	+	7	6 mos.	4-5	-	-	+	+	+
3. L. R.	+	65	6 yrs.	7	+	+	+	+	-
4. S. R.	-	0	-	7-10	-	-	+	-	-
5. P. G.	-	0	-	?	-	-	-	-	-
6. E. G.	+	35	6 mos.	20	+	-	+	-	-
7. A. S.	+	23	2 mos.	6-10	+	+	-	-	-
8. M. S.	+	35	2 mos.	7-10	+	-	-	-	-
9. W. B.	-	21	4 mos.	?	-	-	-	-	-
10. S. M.	-	5	1 yr.	?	-	-	-	-	-
11. F. T.	+	30	1 mo.	5-7	-	-	-	-	-

was probably due to recurrence of disease three years after resection. In addition five patients had edema of the lower extremities and showed evidence of severe vitamin B complex deficiency such as stomatitis, glossitis, cheilosis and peripheral neuritis. Three had tetany, three had frequent episodes of abdominal pain, two had moderate abdominal distention and only one showed clubbing of the fingers.

HEMATOLOGIC FINDINGS

Patients 1 through 4 had hemoglobin levels of 9 gm. per cent or less following resection (Table III). In no instance was a macrocytic anemia found. Bone marrow aspirations performed in three patients were compatible with the findings in the peripheral blood. The white blood count was normal in every instance and in the two cases in which platelets were counted they were present in adequate numbers. The prothrombin time was prolonged on one occasion and was promptly corrected by administration of vitamin K. Serum iron determinations were done in patients 1 through 4. Three had serum concentrations of 86, 51 and 33 micrograms per cent, respectively. In the presence of a normal iron binding capacity of the serum, these figures are compatible with the diagnosis of iron deficiency anemia. The fourth case had a normal serum iron. The Schilling test for vitamin B₁₂ absorption using radioactive Co⁶⁰ or Co⁵⁸ was performed in three patients by Drs. Sanford Oxenhorn and Solomon Estren. Two of these were incapable of absorbing orally administered, labeled vitamin B₁₂ while in the third, absorption was normal.

GASTROINTESTINAL STUDIES

Histamine achlorhydria was noted in one patient, while five others tested showed the presence of free hydrochloric acid in the gastric contents. Three patients had pancreatic enzyme studies performed by Dr. David Dreiling. The duodenal specimens were studied for total volume, maximum bicarbonate con-

Case No.	Hb. (gm. %)	R. B. C.	Serum Fe. μg./%.	Serum IBC† μg./%	Bone Marrow	Bic. Ab- sorption	Prothrombin time sec. (Control)	Gastric acidity, Units‡		Pancreatic Secretin Studies§			Roentgen Studies
								Free	Total	Vol. Ml.	Bicarb. Conc.	Amylase u./kg.	
1. S. K.	6.8	2.0	86	321		0	18 (11)	0	20	2.5	61	4.3	T. T. 15 min. to right side of colon
2. D. H.	6.6	2.9	51	363	Mild granu- locytic hyper- plasia		13 (11)						T. T. 15 min. to transverse colon
3. L. R.	4.3	1.7	33	259						2.9	60	4.9	Diffuse inflamma- tory disease of almost entire small bowel— marked dilatation of colon
4. S. R.	9.0	3.6	156	320	Slight eryth- roid hy- perplasia	Normal	14 (12)	50	70	3.6	136	6.6	T. T. 30 min. to colon; jejunum dilated
5. P. G.	13.6												
6. E. G.	12.3	4.0						45	70				T. T. 1 hr. to co- lostomy opening
7. A. S.	10.0	3.7			Hypocellu- lar marrow	0	14.5 (12)	60	80				Barium in colon in 15 min.
8. M. S.	13.0	3.8						30	45				Barium in colon in 60 min.
9. W. B.	10.8	3.9					15 (12)						Barium in colon in 60 min.
10. S. M.	10.2	3.8						64	78				Barium in colon in 60 min.
11. F. T.	10.7	3.7					14 (13)						T. T. 15 min; dila- tion of jejunum

* Lowest levels recorded.

† IBC = Iron binding capacity.

‡ After histamine.

§ Lower limits of normal: vol., 2.0 mL/kg.; Bicarb. conc., 90 mEq./l.; amylase 6 μ/kg.

¶ T. T. = Transit time.

centration and enzyme concentration. The total volume was normal in all three patients although two had low bicarbonate and enzyme values (Table III).

Roentgen studies of the gastrointestinal tract performed at various intervals after operation, showed rapid transit time in all patients studied. Barium administered orally appeared in the colon in 15 minutes in three patients, in 30 minutes in one, and in the remaining four, the transit time was one hour. Patient 3 was noted to have diffuse disease of the entire jejunum and ileum with multiple fistulous tracts. Marked dilatation of the bowel was noted in only two cases. Patient 6 had a well functioning colostomy and afforded the opportunity to study the effect of calcium carbonate on the transit time. A butter-rice barium meal was administered first without calcium carbonate and then with the agent added, and the length of time required for the meal to appear at the colostomy site was noted. A significant delay in the transit time was noted when calcium carbonate was added.

Five patients had roentgen studies of the skeletal system and all five showed osteoporosis and/or osteomalacia to some degree. In addition to marked decalcification, roentgen studies in patient 2 showed narrowing of the interspace between the second and third cervical vertebrae, and a chip fracture of the right hip.

CHEMICAL STUDIES OF THE SERUM

Six of eight patients tested had albumin concentrations of 3 gm. per cent or less and five of the six had reversal of the albumin globulin ratio (Table IV). Six of the eight had serum calcium concentrations below 8.5 mg. per cent; three manifested tetany during the early postoperative months. Serum alkaline phosphatase concentration was elevated in two of seven patients studied, probably due to osteomalacia. Serum cholesterol levels were low in two of five patients tested (120 and 123 mg. per cent).

TABLE IV
Chemical analyses of serum

	Serum Proteins Gm%*		Globulin	Ca mg.%*	P mg.%	Alk. Phos.† K-A u.	Cholesterol mg.%*
	Total	Albumin*					
1. S. K.	5.3	2.0	3.3	6.4	2.6	19	120
2. D. H.	6.2	2.9	3.3	7.5	2.5	16.7	
3. L. R.	3.9	2.2	1.7	8.2	2.2	9	
4. S. R.	6.4	2.3	4.1	10.6	3.1	11.1	123
5. P. G.							
6. E. G.	6.9	4.3	2.6	10.4	2.3		
7. A. S.	7.4	3	4.4	7.8	3.7	10.2	174
8. M. S.	5	4.6	2.9	8.5	3.2	7.7	180
9. W. B.							
10. S. M.							
11. F. T.	6.7	2.4	4.3	7.2	2.2	10.9	165

* Lowest levels.

† Highest levels recorded.

TABLE V
Tests of intestinal absorption

Case No.	Time After Resection	Oral Glucose Tolerance Test (100 gm. Glucose) Blood Sugar, mg. %					Vit. A Tolerance Test† Serum Vit. A, mg. %				Serum Carotene Level, $\mu\text{g. \%}$	Fecal Fat, % Dry Wt.*†
		0	30 min.	60 min.	120 min.	180 min.	0	4 hrs	6 hrs	8 hrs		
1. S. K.	1 mon.	95	96	100	95	86	56	58	52	44	8	55.8(41.7)
	6 mos.	94	123	130	100	95	54	102	183	108	14	
	4 yrs.	86	92	96	85	74	44	44	176	120	3	
2. D. H.												+
3. L. R.	8 yrs.	98	116	102	108	113	13	15			14	56.4(20.8)
4. S. R.	17 yrs.	75	137	119	74		84	157	149	152	16	+
5. P. G.												
6. E. G.	8 mos.	80	138	116	128	60	38	95	158	158	113	42.8(36)
7. A. S.	9 mos.	102	114	90	78	85	46	31	38	34	34	19.99(15.39)
8. M. S.	7 mos.	89	120	102	88	70	87	165	154	136	56	+
9. W. B.	4 mos.	72	102	119	64	72						
10. S. M.	3 yrs.	86	120	125	68	70	87	143	332	180	117	+
11. F. T.	1 mo.	90	113	129	121	105	34	39	33	35	17	+

* Fatty acid fraction shown in parentheses.

† Plus mark indicates presence of steatorrhea on microscopic examination.

‡ 180,000 U. Vitamin A in oil.

STUDIES OF INTESTINAL ABSORPTION

All stool specimens examined microscopically showed steatorrhea; the fecal fat content consisted mainly of fatty acids with lesser amounts of soaps and neutral fats. Quantitative determinations of fecal fat were performed in four patients. Fecal fat ranged from 20 to 56.4 per cent of the dry stool weight (Table V).

Glucose tolerance tests were performed in nine patients. In only two were the curves normal. Five had flat absorption curves, while two showed evidence of impaired absorption. One of the former, patient 1, had the test repeated after receiving ACTH for several months and showed evidence of increased absorption. After discontinuation of steroid therapy, a flat curve was again obtained.

Vitamin A absorption tests were done in eight patients. In three patients the vitamin A absorption curve was flat and in five any deficiency in the ability of the bowel to absorb fat was not discernible. Three of the five patients had normal fasting serum vitamin A levels. Patient 1 had three vitamin A tolerance tests, one month, six months and four years postoperatively. The first was flat, the second and third were normal. Carotene determinations were obtained in eight patients and normal levels were found in three. These three had normal fat absorption measured by the vitamin A tolerance test.

DISCUSSION

There is a wide variation in the manner in which patients react to small bowel resection (3). There are many exceptions to the simple rule that the more extensive the resection, the more severe the intestinal "insufficiency". The condition

of the remaining bowel is the most important factor in determining the post-operative fate of the patient. If disease remains or recurs in the residual bowel, the outlook may be gloomy indeed.

There are two additional factors which are perhaps not as well appreciated in determining the prognosis following resection. The first is the presence of a sufficient length of colon. Although the large bowel does not play an important role in the absorption of the three main nutrients, it acts as a reservoir and by adequate absorption of water and electrolytes, can alter the consistency of the stools. It also alters the acidity of the stools by bacterial decomposition of food. Since diarrhea is the most prominent symptom after resection, leading to weight loss, inanition, and water and electrolyte depletion, all attempts should be made to preserve the absorbing surface of the right side of the colon. This principle was used to good advantage in case 2 where jejuno-transverse colostomy had resulted in profuse diarrhea which began in the second postoperative month. In an attempt to increase the absorptive surface of the colon, the original anastomosis was replaced by one in which jejunum was anastomosed to the ascending colon, thereby adding one foot to the absorptive surface of the colon. This was effective not only in reducing the number of the stools but also in changing their consistency.

A second factor which is frequently overlooked is the psychologic status of the patient. Personality studies of patients with regional enteritis indicate that emotional factors may play a considerable role in the production and progress of the disease (4, 5). One can readily see how an undesirable sequence of events may ensue following resection for ileitis. If "psychogenic hypermotility" is present, it will not only add to the already existing impairment of absorption but may perhaps enhance the structural changes in the remaining small bowel.

With the exception of these two variables and the three factors mentioned above, the sequelae of massive resection are proportional to the magnitude of the resection. Resections of 85 per cent or more of the small bowel resulted in intestinal "insufficiency". Patients 1 and 7 had such severe nutritional disturbances that, were it not for steroid hormone therapy, they would certainly be relegated to the role of intestinal cripples. The group with 50 per cent or less of the bowel resected, exhibited no severe nutritional difficulties with the exception of patient 3. This patient had a resection of seven feet of small intestine and went into remission for three years, only to have a recurrence of the disease throughout the remaining jejunum and ileum. At present he is a poor surgical risk and his prognosis is grave.

Anemia was not an outstanding clinical feature after massive intestinal resection as reported in the literature, and when it occurred it was usually the result of some complicating factor such as diffuse carcinomatosis or the presence of a blind intestinal loop (6). In our series, anemia played a predominant role in three patients, all of whom had resections for jejuno-ileitis. There were probably numerous factors that kept the hemoglobin subnormal. Patients 1 and 2 were suspected of having recurrent disease on many occasions as a cause for the anemia, but this was never demonstrated radiographically. The patient in case 1

experienced an episode of blood loss, due perhaps to stomal jejunitis or to hypoprothrombinemia. His poor nutritional status was probably responsible for frequent non-specific, intercurrent infections combined with vitamin K deficiency. Patient 2 required monthly transfusions in addition to supportive therapy for an iron deficiency anemia first noted four years after resection. Inadequate iron absorption was assumed to be the etiologic factor. There was no evidence of hemolysis; the stools were negative for occult blood; and roentgen studies failed to show recurrent disease. The anemia in case 3 was caused by diffuse disease of the small bowel with repeated massive hemorrhages, a situation analogous to bleeding in ulcerative colitis. The possibility that his bleeding was perhaps due to the presence of a small blind loop created when resection of a portion of the jejunum was followed by side-to-side anastomosis received consideration. The anemia produced by a blind loop however, is usually macrocytic (6).

The defect in the external secretion of the pancreas is probably due to fibrosis secondary to malnutrition. Since secretin is produced almost entirely in the upper intestine, a deficiency of this hormone may result from either extensive resection or disease of the small bowel mucosa (Cases 1 and 3, respectively). The external secretion of the pancreas was further hampered by achlorhydria in patient 1. It is noteworthy that, despite a generalized deficiency of digestive secretions as indicated by achylia gastrica with diminution of pancreatic bicarbonate and amylase, the intestinal absorption of lipids in case 1 returned towards normal as indicated by the vitamin A tolerance test.

Case 1 afforded an opportunity to study the effects of severe dehydration, starvation and loss of potassium on renal function. Six months after operation, the urine was noted to contain albumin, many white cells were present in the sediment and the specific gravity was fixed at 1.010. These findings suggested the possibility of intrinsic renal disease. Further investigation led to the presumptive diagnosis of renal tubular acidosis as a result of long standing dehydration, reduction of renal blood flow, chronic hyponatremia and possible hypokalemia. The fact that the kidneys were capable of conserving sodium was good evidence that adequate renal function existed. There was evidence to suggest depressed adrenocortical function such as muscular rigidity and cramps, stiffness and hypotension.

The reaction of the feces was usually acid. Failure to secrete a normal amount of intestinal juice due to the loss of so much intestine might have led to poor neutralization of acid gastric chyme. This factor together with the presence of free fatty acids accounted for the acidity of the feces. The low pH of the feces was especially marked in patients 1 and 3, both of whom had reduced pancreatic secretions.

Microscopic examination showed the presence of large numbers of undigested meat fibers. Fat globules and fatty acid crystals could be seen along with neutral fats. In most instances the fat was hydrolyzed in the small bowel, but there was marked impairment in absorption of fatty acids. The extent of steatorrhea was striking in some patients, amounting to 56.4 per cent of the dry stool in one instance.

The outstanding nutritional difficulty after massive resection is the absorption of fats (7-10). This has been documented by metabolic balance studies as well as other tests that measure the intestinal absorption of lipids. The use of the vitamin A tolerance test and the concentration in the serum of the vitamin A precursor, carotene, stem from our knowledge that the absorption of fat soluble vitamin A from the gut is governed by the principles that determine the intestinal absorption of fat. The desirability of using the vitamin A tolerance test instead of the time-consuming and highly technical balance studies received further impetus from the work of Legerton (11) who found a fairly regular relationship between the degree of fat absorption as determined by balance studies and the height of the vitamin A level in the serum, as determined four to six hours after a standard test dose. If the peak of a somewhat flat curve is reached at eight hours, it is indicative of retarded absorption.

The fasting level of vitamin A in the serum is of importance as well as the elevation of the serum concentration after oral intake of vitamin A in oil. The small absorbing surface readily leads to a deficiency of vitamin A as well as other vitamins, which may in turn lead to impaired intestinal absorption, thus creating a cycle in which poor intestinal absorption because of the absence of most of the intestine leads to deficiencies which further enhance absorptive difficulties.

It is almost unanimously held that there is little evidence of malabsorption of carbohydrates in cases of massive resection (9, 10), despite the flattening of the glucose tolerance curve.

Experimental evidence reveals a very definite difference in fat absorption after proximal and distal small bowel resections; increased loss of fat in the stools was noted after ileal resections (12). Protein absorption is influenced also to a greater degree by the ileal resections, although nitrogen losses in the stool were never as marked as fat losses. Only one of our patients (case 3) had a proximal bowel resection and he suffered no ill effects. The distal small bowel is involved much more often in inflammatory processes as well as in vascular accidents, accounting perhaps for the nutritional disturbances seen after massive resections.

The presence of an intact ileocecal valve is of great importance following extensive resection, particularly if it involves the distal small bowel. Patient 4 had 50 per cent of the distal small bowel resected and, except for diarrhea which has not been incapacitating, has shown little if any evidence of malabsorption. Since the ileocecal valve was not resected, it continued its function of delaying the rapid passage of food into the colon thus assuring greater absorption in the ileum.

GENETIC ASPECTS

Familial occurrence of regional enteritis and enterocolitis has been well documented (13). There have been a considerable number of reports of the disease occurring in close blood relatives, e.g., in three siblings, in mother and daughter, or in father and son (14, 15). The family history of patient 1 is noteworthy, since four close blood relatives were found to have this disease. The mother of the patient showed definite involvement of the terminal ileum roentgenologically. Two younger brothers had the diagnosis confirmed at operation; one of them

had an ileotransverse colostomy for regional ileitis and ulcerative colitis. The other had a partial jejunectomy for diffuse disease of jejunum and ileum. The recognition that familial occurrence is not rare in regional ileitis may provide a possible clue to the etiology of the disease. In comparison to idiopathic ulcerative colitis, where the presence of more than one case in the same family is unusual (16), the contrast is striking and perhaps difficult to accept as mere coincidence. One may speculate that the low familial incidence of ulcerative colitis probably excludes contagion and heredity as important factors in the genesis of this disease. In jejuno-ileitis on the other hand, the possibility may be considered that genetic transmission and/or infectious agents are important in the evolution of the disease.

MALABSORPTION SYNDROME FOLLOWING GASTRO-ILEOSTOMY

Gastro-ileostomy is a rare surgical error. The first case was reported in 1915 (17) and by 1947 a total of 27 cases had appeared in the literature (18). In every instance gastro-jejunostomy for peptic ulcer was the intended operative procedure. Analysis of the symptomatology in the 27 cases revealed weight loss in 19, abdominal pain in 17, diarrhea in 14, vomiting in 6, ileal ulcers in 6, and hemorrhage in 3. The first reported case of gastro-ileostomy following subtotal gastrectomy appeared in 1951 (19). Symptoms caused by inadvertent gastro-ileostomy following subtotal gastrectomy appear sooner in the postoperative period than following a gastro-enterostomy without resection. When gastro-enterostomy is performed for duodenal ulcer, despite the anastomosis of the stomach to the ileum instead of jejunum, a patent pylorus is preserved, thus assuring the passage of some of the food into the jejunum and increasing the quantity of food absorbed. Following subtotal gastrectomy, if the ileum is anastomosed to the stomach, particularly if lower ileum is selected, unabsorbed food enters the colon rapidly and, since the pylorus has been resected, there is no avenue of escape for absorption of any nutrients. Steatorrhea and other features of the malabsorption syndrome soon appear. Until the mistake is identified and corrected, the sequelae are exactly the same as those following massive resection.

One possible clue to the diagnosis of gastro-ileostomy in a patient manifesting diarrhea and weight loss after a subtotal gastrectomy is the presence of a flat glucose tolerance curve. The occurrence of a flat curve was noted in a previously reported instance of gastro-ileostomy (20) and in patient 12 led us to suspect the correct diagnosis before roentgen studies were performed. In a patient with a properly performed Billroth II operation, the oral glucose tolerance curve is normally characterized by an early peak followed by a sharp drop to hypoglycemic levels (21). In contrast, the finding of impaired intestinal absorption of glucose should make one suspect gastro-ileostomy.

ANALYSIS OF VARIOUS THERAPEUTIC REGIMENS

Dietary Measures. The diet should include a liberal quantity of carbohydrate since this nutrient is well absorbed. Some starches causing fermentation and abdominal distention should be avoided. The protein intake should be moderate

to high. Fat is poorly tolerated and patients will voluntarily restrict this food-stuff to a minimum. Resection of the small bowel leads to a low calorie intake thus depressing the basal metabolic rate. Reduction in caloric and other metabolic requirements is an important compensatory factor in keeping patients who have had massive resections alive. Our patients did not care for pureed foods and did better on whole foods. Similar observations have been made by other investigators (10). A plausible explanation for this perhaps is that foods enjoyed by the patient stimulate a greater flow of digestive ferments. One must never overload the bowel to the point of fatigue, however.

Supportive Therapy. Calcium should be administered routinely following extensive small bowel resection. When hypocalcemia exists the parenteral as well as the oral route should be utilized until normal calcium balance is restored. Iron deficiency should be corrected by the use of ferrous salts. It is understandable that oral iron medication is often ineffective after massive resection in treatment of iron deficiency anemia, whereas adequate doses given parenterally are apt to produce dramatic results. The parenteral preparation most extensively used is saccharated oxide of iron which must be administered intravenously. Recently, a new iron-dextran complex which can be given intramuscularly has been shown to be similarly effective in hemoglobin regeneration (22). This can be given in large doses and increases the safety of parenteral therapy. If megaloblastic anemia is present, vitamin B12, liver extract, and/or folic acid therapy is indicated. In presence of marked hypoalbuminemia, daily infusions of salt-free albumin combined with high protein intake proved to be of great benefit in our experience. Keeping the blood count normal and maintaining a normal level of plasma protein will undoubtedly assist in improving the absorption of important elements through the intestinal mucosa. Many patients exhibit multiple vitamin deficiencies while diarrhea and steatorrhea are active. Evidence of deficiency of factors of the vitamin B complex is most common, but evidence of the lack of vitamins A, D, E and K as well as of ascorbic acid, may be present. Thus therapy should include multivitamin preparations. Hemorrhagic manifestations caused by hypoprothrombinemia usually respond well to adequate parenteral vitamin K therapy. Occasionally, even massive doses of vitamin K fail to raise the serum prothrombin level, necessitating multiple blood transfusions.

Steroid Therapy. Much evidence has been accumulated to show that adrenocortical hormones exert an effect on intestinal absorption of fat and fat-soluble vitamins. Adlersberg and co-workers noted clinical improvement manifested by increased sense of well-being, improved appetite, disappearance of diarrhea and weight gain in patients with idiopathic sprue who had been refractory to other forms of therapy (23). Absorption studies following the use of steroids in sprue patients showed a diminution in fecal fat excretion and increased in serum vitamin A level, although the vitamin A tolerance curve did not change much. Other investigators, on the other hand, found that the fecal excretion of fat sometimes increased during the treatment with hormones, and the flat vitamin A tolerance curve characteristic of sprue was markedly raised during the adminis-

tration of ACTH (24). These paradoxical observations were explained by a dual effect of the hormone producing increased intestinal absorption as well as an increased enteric excretion of endogenous fat (26).

The steroids were used in two of our patients for the purpose of improving intestinal absorption with gratifying results. Patient 1 presented a serious nutritional problem until ACTH was started three months after resection. Prior to the use of corticosteroid therapy he had to be readmitted on two occasions because of starvation, dehydration and inanition. During his third postoperative admission, ACTH, 80 mg. daily, was administered by intravenous drip. This produced a ravenous appetite. His strength improved and he gained seven pounds in two weeks. After discharge, he remained on a small daily maintenance dose of steroid hormone. When he was again admitted three months later because of hypocalcemic tetany, his vitamin A and glucose tolerance tests, which were flat shortly after operation, now indicated markedly improved intestinal absorption. When steroid therapy was discontinued, his glucose tolerance test again became flat. He was started on prednisone (15 mg. daily) in March 1955 and in the ensuing year gained 20 pounds. His stools are formed, he feels better than he did since resection and believes that he is ready for gainful employment.

Patient 6, like patient 1, was left with only 18 inches of small bowel. After surviving her resection and postoperative cholecystectomy, she returned to the hospital because of diarrhea, weight loss and tetany, all of which were referable to the disturbances caused by the extensive resection. She was treated with cortisone, and within four days her weight improved and diarrhea subsided. She had not had any significant difficulty since, receiving a maintenance dose of prednisone in addition to vitamins.

Studies on the role of the adrenal cortex in intestinal absorption have thus far been inconclusive. Adrenocortical hypofunction has been suggested as the cause of steatorrhea (25), but no abnormalities have been noted in the adrenal glands in patients with sprue. Many patients with Addison's disease have diminished intestinal absorption, however (26). Whatever the underlying mechanism may be, the improved sense of well-being and cheerful mental outlook which happens to most patients receiving steroid for any condition and the enormously increased appetite with resultant improvement in nutrition are beneficial effects which are particularly desirable after massive bowel resection. The improved emotional state may be helpful to these patients who are often depressed. The mere fact that marked improvement in diarrhea and sense of well-being can occur so promptly with a new drug after all other forms of therapy are unavailing may give hope and optimism to a discouraged patient and thus act as a crutch providing a sense of security.

Complications attending the therapeutic use of corticotropin and the cortisones over a prolonged period must be guarded against. The detection and management of acute infections in patients receiving steroid therapy is a challenging clinical problem. The low resistance to infections and stress of patients who

have had extensive resections is well known. In addition, the manifestations of infection may be masked by corticosteroid therapy. Therefore, full attention should be given to minor symptoms and signs of infection.

The negative calcium and/or nitrogen balance associated with steroid therapy may result in intensification of the pre-existing osteomalacia or osteoporosis. Multiple fractures including compression fractures of the vertebrae may occur. The refractory iron deficiency anemia (patient 2) might be aided by corticosteroid therapy, but, in view of the marked changes already present in her skeletal system, one would hesitate before beginning this therapy.

IS MASSIVE RESECTION FOR JEJUNO-ILEITIS WARRANTED?

The course of jejuno-ileitis is variable. It may be very mild with little tendency to fever, weight loss or other general systemic manifestations. On the other hand, severe forms of the disease may produce general toxemia, marked weight loss and loss of appetite. The inflammatory changes in the intestine interfere with the absorption in the involved loops and the irritating effect of the disease on the entire gastrointestinal tract produces hypermotility and further impairment of absorption. Arrest of the disease may be achieved in certain cases of ileitis after resection. However, there is a distressingly large group of patients who have lost a large part of intestine through resection and then have further activity of the disease with disturbance of the function of the remaining bowel. A recurrence rate as high as 34 per cent has been reported; most of the recurrences occurred within two years after resection (27). The question of serious nutritional difficulties has frequently been a factor limiting the extent of resection. Kiefer (27) stressed the importance of secondary, tertiary and even fourth resections in the aggressive attempt to eradicate disease. One-third of his patients, subjected to secondary operations, had relief of ileitis but at the expense of the nutritional status. The severe absorption defects resulted in "intestinal invalidism" in some. Numerous resections or one massive resection which leaves the patient a nutritional cripple can hardly be considered a cure of the disease. Cattell (28) suggested a planned multiple stage procedure of intestinal resection on the basis that patients can be maintained in a better nutritional status. An alternative procedure is jejuno- or ileo-colostomy with exclusion of the diseased bowel followed by resection six months later if necessary.

Experience seems to indicate that surgical intervention should be confined to those cases complicated by obstruction, abscesses or fistulas and those in which a most thorough medical regimen has failed. When an indication for surgery arises the less radical procedure of side tracking and exclusion is probably the operation of choice. The mortality and recurrence rates are lower than after extensive resection (29). The side tracking operation frequently obviates the need for future resection by excluding the diseased bowel from the fecal streams. The inflammatory process usually subsides when the bowel is put to rest. If the excluded bowel fails to heal, or disease recurs and medical therapy does not halt the progress of the disease, massive resection is warranted and is facilitated by the fact that a large portion of the bowel has not been functioning for months preceding resection.

After extensive resection the ability of the bowel to absorb fats is impaired to a greater extent than absorption of the other nutrients. In addition, lipids are the last of the food substances to show improved absorption, as measured by vitamin A tolerance and balance tests, after resection. The ability of corticotropin and the cortisones to improve absorption of lipids has been well documented (30) and unless a strong contra-indication is present these hormones may be administered in the early postoperative period, as soon as steatorrhea becomes evident, as well as later along with dietary and replacement therapy. Steroid hormones also seem to promote absorption of carbohydrates, calcium, vitamin K and hemopoietic substances (31).

SUMMARY

1. Eleven cases of extensive resection of the small intestine are presented. Five of the resections were for jejuno-ileitis, the remainder for acute vascular conditions necessitating emergency resection.

2. Nine patients have been under observation for periods varying from two to 13½ years, one was lost to follow-up after two years and one died.

3. Diarrhea, steatorrhea, weakness and considerable weight loss were the postoperative sequelae encountered most often. Other frequent findings were abdominal pain, tetany, edema, osteoporosis, anemia, hypoproteinemia, hypocalcemia, low serum vitamin A and carotene levels, and flat glucose and vitamin A tolerance curves.

4. Despite numerous variable factors, the most important of which is the status of the remaining bowel, the severity of the sequelae is proportional to the magnitude of the resection.

5. ACTH and the cortisones have a beneficial effect on intestinal absorption and should be used when malabsorption appears in the early postoperative period and later, if necessary.

6. A case report of a patient on whom an inadvertent gastro-ileostomy was performed is presented and the results of exclusion of almost the entire small bowel is discussed. The oral glucose tolerance test may prove useful in differentiating between gastro-ileostomy and gastro-jejunostomy when diarrhea and weight loss persist after subtotal gastric resection.

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In Memoriam

With the death of Dr. Ira Cohen, another of the distinguished medical men who helped to make The Mount Sinai Hospital a great medical institution passed from the scene. What makes a good medical center is the quality of teaching that it gives to its resident and junior attending staff. In this Dr. Cohen excelled. He was an excellent teacher, beloved by all the younger men for whom no effort was too great to improve their education and their surgical ability. He possessed unusual intellectual and personal integrity. Upon his death, letters were received from all over this country and abroad from the men and women whom he had taught and befriended.



DR. IRA COHEN

1887-1957

Dr. Cohen was born in Long Branch, N. J. in 1887. His father was Maurice Cohen and his mother Rosalie Meyer. He was graduated from Columbia University in 1909 and received his medical degree in 1911. He interned at The Mount Sinai Hospital from 1911 to 1914 and was Adjunct Surgeon from 1920 to 1932. In 1932 he was appointed Attending Neurosurgeon, which position he held until his retirement in 1950 when he became Consulting Neurosurgeon.

For many years Dr. Cohen was president of the Medical Board of The Mount Sinai Hospital, which is the highest honor that the hospital can bestow. He was known for his justice and foresight and filled that position with great credit for many years. It was said of Dr. Cohen that if some question arose involving a member of the staff, it was better not to stress friendship, as he tended to lean over backward for fear of appearing to be influenced in his judgment by his friendship for the colleague.

He served in the army, first on the Mexican border, then as Surgeon to Base Hospital #3 (The Mount Sinai Unit) with the rank of major. He established a complete hospital at LeBraun, France, and outfitted and ran that hospital with distinction. He was retired with the rank of Colonel in the Medical Reserve Corps and was in the Reserves until his death.

Dr. Cohen was a Diplomate of the American Board of Surgery and Neurology, a Fellow of the American College of Surgeons, a member of the American Medical Association, New York Academy of Medicine, The American and New York Neurological Societies, The New York Surgical Society and the Order of World Wars. He was the author of over thirty scientific papers.

Dr. Cohen is survived by his widow, Dorothy Dreyfuss, whom he married in March 1927.

FOR THE EDITORIAL BOARD

COMA DUE TO AMMONIA INTOXICATION FOLLOWING PORTACAVAL SHUNT FOR ESOPHAGEAL VARICES

RECOVERY FOLLOWING TREATMENT WITH LARGE DOSES OF SODIUM
GLUTAMATE

VERNON A. WEINSTEIN, M.D.*

INTRODUCTION

The role of ammonia in the pathogenesis of hepatic coma is still a subject of considerable debate. In some cases, especially those associated with liver failure, there are unquestionably several contributing factors, of which ammonia may play a role of varying importance.

There seems to be, however, a group of coma cases in which the liver is merely by-passed rather than in failure. In these it would seem that ammonia plays the dominant causative role.

The value of glutamic acid therapy for hepatic coma has been both condemned and defended in various clinics so that its usefulness is an open question. The following case has direct application to these controversial subjects and is therefore deemed worthy of reporting.

CASE REPORT ML 3721

The patient is a 52 year old married female who was first admitted to The Mount Sinai Hospital for diagnosis January 1, 1953. Her past history included severe bronchial asthma, obesity and hypothyroidism. There was no history of intestinal symptoms or abdominal pains. Two weeks prior to admission, a sudden onset of hematemesis and fainting required hospitalization at another institution, where she received blood transfusions and other supportive therapy. Physical examination revealed a pale, obese middle-aged woman, not acutely ill, with slight edema of the eyelids and asthmatic wheezes throughout the chest. The liver and spleen were not palpable nor were there any prominent veins of the abdominal wall. Laboratory tests revealed a moderate secondary anemia; alkaline phosphatase—4 King Armstrong units; icterus index—3; cephalin flocculation +; thymol turbidity—6.7; total protein—7.7 grams per cent; albumen—4.2 grams per cent; globulin—3.5 grams per cent; cholesterol—430 mgm per cent; esters—340 mgm per cent. X-rays of the gastrointestinal tract revealed numerous large esophageal varices, but no other lesion.

She was treated for asthma and hypothyroidism, with occasional recurrence of symptoms, until May 31, 1956, when she was readmitted to The Mount Sinai Hospital for weakness, dizziness and melena of three days duration. On the day of admission, she vomited a large quantity of bright red blood. Physical examination revealed an obese, pale female in moderate shock. The pulse was rapid, blood pressure 80/60, the abdomen soft and not tender. The liver and spleen were not palpable. The hemoglobin was 9.3 grams, and the white cell count and differential were normal. A Sengstaken-Blakemore tube was inserted, the esophageal and gastric balloons inflated, and the bleeding was controlled. Twenty-four hours later, the esophageal balloon was decompressed, and twenty-four hours after that, the tube was removed without recurrence of bleeding.

Blood chemistry determinations on June 1, 1956 revealed blood urea nitrogen—31 mgm per cent; bilirubin total—0.6 mgm per cent; 1 minute bilirubin—0.15 mgm per cent; alkaline phosphatase—4.6 King Armstrong units; cephalin flocculation 1+; thymol turbidity

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—2.3 units; total protein—6.4 grams per cent; albumen—3.3 grams per cent; and globulin—3.1 grams per cent. The prothrombin time was 13.5 seconds with a control of 14.5 seconds, and the BSP showed 6% dye retention.

An x-ray of the gastrointestinal tract showed even more extensive varicosities than were present 3½ years ago (Fig. 1). No other lesion was seen in the stomach or esophagus.



FIG. 1. Esophagram taken before operation revealed numerous varices of esophagus and cardia of stomach.



FIG. 2. Esophagram taken 6 months after portacaval shunt failed to reveal varices in esophagus, although there are a few in the stomach.

A percutaneous splenogram was performed which revealed the following: The splenic vein filled well and appeared approximately normal in size. The coronary vein was quite wide. Tortuous veins were seen in the region of the fundus of the stomach and mediastinum. The portal vein was about 1 inch in diameter and showed no evidence of filling defect. The dye seemed to enter the liver (Fig. 3).

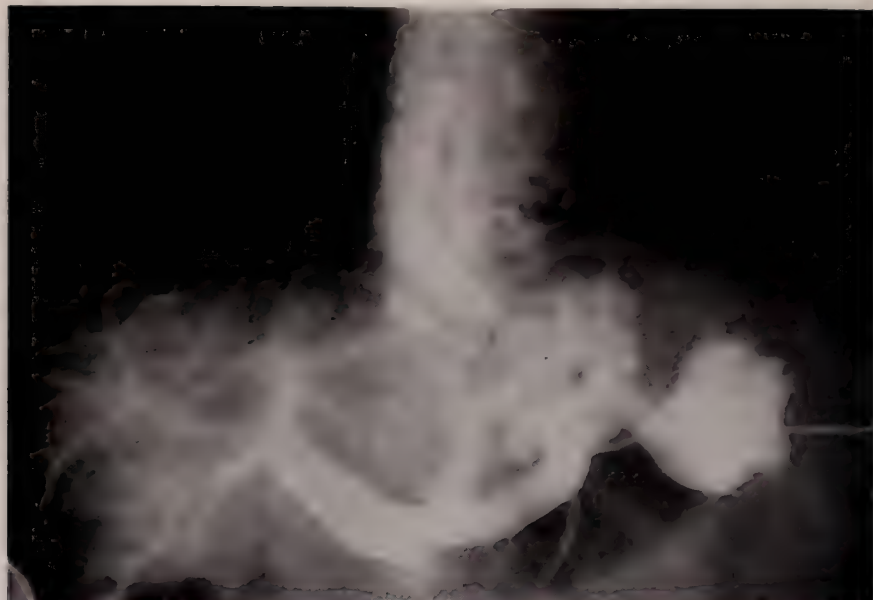


Fig. 3. Percutaneous splenogram taken prior to portacaval shunt. At extreme right the needle may be seen entering the spleen which is partly opacified. The splenic and portal veins are well outlined. A large tributary entering from above is the extremely dilated gastric coronary vein, which connects with numerous varicosities of the gastric cardia and esophagus.

In view of the facts that the patient had bled on two occasions from esophageal varices, that liver function was good and that the portal vein was normal, decompression of the portal system by portacaval shunt was deemed both feasible and advisable. This was successfully performed by the author on June 14, 1956. A right thoracoabdominal approach was used. The initial portal venous pressure taken in a right gastroepiploic vein was 480 mm of saline. (Normal pressure is 200 mm. or less. The liver was smooth and only moderately enlarged. The spleen was three times normal size. Further abdominal exploration revealed no additional pathology. An end-to-side portacaval shunt and liver biopsy were performed.

Jejunal vein pressure taken immediately after the shunt was 280 mm of saline, representing a fall of 200 mm. The liver biopsy was reported normal liver tissue with no evidence of cirrhosis.

The patient made a good operative recovery. The wound healed well. However, on the 12th postoperative day, June 26, 1956, the patient was found wandering in the hospital corridor confused and disoriented. The confusion progressed to stupor and by that evening she was deeply comatose. There was no flapping tremor. Barin-kl reflexes were equivocal at first, and then became positive. A diagnosis of ammonia intoxication was made. Blood chemistry determinations confirmed this impression and also demonstrated a marked metabolic alkalosis and hypocalcemia. See Table I.

Therapy. Therapy was instituted as follows: (1) 190 grams of L-sodium glutamate was given intravenously and 80 grams of glutamic acid was instilled through a gastric tube within the first 36 hours. (2) 300 meq of potassium chloride was given by vein in the same period. (3) Attempts to eliminate the intestinal source of ammonia were made by repeated catharsis with magnesium sulfate and enemas. In addition, 500 mgm of neomycin was given intravenously every 8 hrs in an attempt to reduce intestinal bacterial activity. (4) A high carbohydrate intake, chiefly in the form of 10% glucose in distilled water, was

venously, was maintained. (5) Careful nursing care was scrupulously administered. This emphasized frequent changes of position and thorough repeated tracheal suction.

Course. A generalized convulsion lasting 8 minutes occurred 36 hours after the onset of coma. The patient continued deeply comatose for 2 days. At times, she appeared moribund except that her pulse was full and blood pressure normal. On the morning of the third day, she began to react. There were protective movements to painful stimuli and the gag reflexes returned. She began to vocalize. On the morning of the 4th day, June 30, 1956, consciousness returned. Drowsiness and considerable confusion persisted for several days but gradually cleared. A low sodium, low protein diet was prescribed. Cathartics were given frequently and glutamic acid and potassium triplex were given by mouth. Marked weakness, peripheral edema and bronchial congestion were troublesome and were only partially improved by the time she left the hospital July 17, 1956.

Follow-up. Since that time, she has continued to be troubled by peripheral edema and weakness. When seen August 28, 1956, her family claimed that she was still not mentally clear. The blood ammonia level on that day was 3.4 micrograms/cc and the blood pH was 7.4. Strict limitation of dietary protein was enforced. Glutamic acid, neomycin, sulfathalidine, mercurial diuretics and thyroid extract were given.

The patient was readmitted to The Mount Sinai Hospital October 26, 1956, complaining of asthma, edema, weakness and mental sluggishness. Steroid therapy for her asthma was given. A repeat barium meal x-ray examination failed to show esophageal varices although a few varices were seen in the fundus of the stomach. The blood ammonia level at this time was 1.5 micrograms/cc (See Table 1). Electroencephalogram was normal.

Examination November 15, 1956 showed the patient markedly improved. She was men-

TABLE I
Summary of chemical determinations following onset of coma

Date	Hematocrit	NH ₃ * micro- gm/cc	Na	K	pH†	Cl	CO ₂ (PCO ₂)	Total Pro- tein	Albumen (Globu- lin)	Urea N	Alk. Phos	Thy- mol Turb.	Bili- rubin	Urine pH
		mEq %	mEq %		mEq %	mEq %	gms %	gms %	mEq %	K.A. U			mg %	
6/26/56		4.90	148	2.7	7.54		35.7							Acid
6/27/56		4.35	148	2.9	7.58	98.1	43.6 (46.4)			13	5.8	1.1	0.6 (0.1)	Acid
6/28/56	40	2.50	146	4.3	7.55		37.7 (42.9)						0.7	Acid
6/29/56	40	3.00	142	3.4	7.45		37.3 (52.0)							Acid
6/30/56														Alkaline
7/3/56		1.75	137	3.2	7.32		38.4 (46.7)	5.8	2.6 (3.2)					
8/28/56		3.40		7.40				7.3	3.5 (3.8)					
10/30/56		1.50		7.48			28.6 (38.0)							

* Normal range 0.4-0.8 micrograms/cc.

† Normal range 7.35-7.40.

Especially noteworthy are the markedly elevated blood NH₃ figures at the onset of coma, and the secondary rise in blood NH₃ which corresponded with a state of mental confusion (8/28/56).

Note also the concomitant low potassium, high pH and acid urine (6/26/56 and 6/27/56).

tally clear. Moderate peripheral edema was still present. Increased doses of thyroid extract were administered. Repeat esophagram December 10, 1956 again failed to reveal esophageal varices (Fig. 2) and the edema and mental state were much improved.

The cause of the portal hypertension in this case is not entirely clear. The venous obstruction was obviously intrahepatic, since a large portal vein was traced to the porta hepatis. Liver biopsy and blood chemistry determinations failed to support a diagnosis of cirrhosis. Until more evidence is forthcoming, we must be content with a diagnosis of "intrahepatic block to the portal system," although we suspect that cirrhosis is the cause.

DISCUSSION

The incidence of ammonia intoxication following portacaval shunting is somewhat difficult to ascertain by review of the literature. Linton (1) states that 3 of the 4 deaths in 72 cases done in the 4 year period 1950-1953 were due to "Liver Failure." Also, in discussing Mc Dermott's paper (2), Linton states that he had seen this complication in relatively few of the 100 cases that he has had to date. Blakemore in the same discussion states that he had 4 patients with transitory periods of dizziness out of 186 shunted cirrhosis cases (2). Mc Dermott described 2 cases of pancreatic carcinoma in which ammonia intoxication occurred following portacaval shunts in the absence of portal hypertension or hepatic disease (2). Rousselot puts the incidence of this complication at a low figure, certainly less than 5% (3). On the Surgical Service of The Mount Sinai Hospital, we have had experience with 3 such complications in the past 2 years.

The present day concept of ammonia intoxication and its relation to "hepatic coma" is the result of the work of many observers over the years, but only recently have some of the problems of the pathogenesis of this condition become clarified (2, 4, 5, 6, 7, 8, 9, 10). It now seems evident that the most important source of endogenous ammonia is that formed in the gastrointestinal tract by bacterial action on the products of protein digestion (11). Another, though less important source, is the kidney, which adds ammonia to the blood stream, as evidenced by the fact that the ammonia content is found to be higher in the renal vein than in the renal artery (2, 12). A third source, and one difficult to measure, is the ammonia produced in tissues generally during deamination processes (2).

The ammonia formed in the intestinal tract is carried to the liver via the portal venous system where most of it is removed. The liver accomplishes this by the synthesis of urea. (13). Confirmatory evidence for this function of the liver is the finding of high levels of ammonia in the portal vein and low levels in the hepatic vein (2, 14). When the liver is bypassed by surgical portal systemic shunts, the ammonia formed in the intestine is found in increased quantities in the peripheral blood (2). The same phenomenon occurs as well in the blood of patients with portal vein obstruction (either intra- or extra-hepatic) in whom natural shunts between the portal and systemic venous systems develop.

An increase in the intestinal source of ammonia in either of the above situations may produce symptoms of ammonia intoxication. It has been shown that hepatic coma or its prodromata can be induced in the cirrhotic patient by ingestion of

ammonium salts, urea, cation exchange resins and even by increased dietary protein (2, 15, 16, 17, 18). Similarly, Mc Dermott has shown that the introduction of whole blood into the intestinal tract of normal dogs causes a rise in blood urea with little rise in ammonia, whereas the same amount of blood introduced into the intestines of dogs whose liver has been by-passed by a portacaval shunt causes no rise in the blood urea, but does cause a marked rise in blood ammonia levels (8). These animals became drowsy and comatose, and a number of them died. Mc Dermott compares these experiments to experiences in the human in which an "innocuous" azotemia occurs following gastrointestinal hemorrhage in the otherwise normal patient, but in the patient with cirrhosis (who has natural portacaval shunts), hemorrhage is often followed by elevated blood ammonia levels and "hepatic" coma.

The cerebral effects of ammonia have been studied extensively (7, 9, 10, 14, 15, 19, 20, 21, 22) and considerable evidence has been adduced that it is the chief offender in hepatic coma. Bessman and Bessman (20) have demonstrated that in patients with liver disease, free ammonia levels in cerebral arterial blood are significantly higher than the levels in cerebral venous blood. These authors state that this implies the conversion of free ammonia to another form by brain tissue. The mechanism of ammonia toxicity is explained on the basis of a disturbance in the Krebs Cycle in which one of the metabolites, alpha-ketoglutaric acid, is depleted. This results in diminution in oxidative phosphorylation and oxygen utilization, and consequently reduced metabolic energy formation (2, 20, 22, 23, 24, 25). The fixation of ammonia with alpha-ketoglutaric acid produces glutamic acid which combines with a second ammonium ion, thus producing glutamine. This also accounts for the apparent discrepancy between elevated blood ammonia levels and its resulting symptomatology since the former must exist for some time before its effects are felt. Similarly the blood ammonia may fall to normal while the symptoms of toxicity persist.

The profound electrolyte disturbances that accompany hepatic coma may be a contributing factor in the production of the symptomatology. Roberts states that this commonly includes respiratory alkalosis, hyponatremia, hypophosphatemia and hypokalemia (26). Schwartz *et al* (10) found no consistent correlation between abnormalities of serum chloride, sodium, potassium, CO_2 or pH and the clinical state although they feel that in individual cases such abnormalities may play a contributing role in production of hepatic coma.

The marked alkalosis evidenced in our case was probably related to the hypokalemia. Low potassium levels have been noted in hepatic coma especially when urinary output is adequate. In the case reported here, this condition obtained and hypokalemia was a dominant feature. The elevated blood CO_2 content is probably related to this factor although impaired pulmonary function also may have contributed to it. This situation is mentioned by Roberts *et al* (26) in their discussion of the electrolyte alterations in hepatic coma. The acid urine, in the presence of an elevated blood pH (Table 1) is typical of hypokalemic alkalosis. The use of the sodium salt of glutamic acid in therapy accentuated the hypokalemia and required even larger doses of potassium chloride than would

have been necessary otherwise. The use of the potassium salt of glutamic acid would have avoided this, but this drug was unobtainable at the time.

In addition to the electrolyte disturbances, excesses of a number of substances such as pyruvic acid, lactic acid and certain amino acids have been considered to be the cause of hepatic coma (27). Certainly to attribute all the manifestations of liver failure to one substance or mechanism would be an oversimplification. However, in this type of case in which the liver is not failing but has been simply by-passed, evidence points chiefly to ammonia as the cause of coma.

Weil-Malherbe (23, 24) found that brain tissue can cause the disappearance of excess ammonia in the presence of glucose and that this is accomplished by the synthesis of glutamine. Sapirstein (28) was able to protect rabbits from the convulsive effects of ammonia by use of glutamic acid. Walshe (29) used monosodium glutamate in treatment of hepatic coma, and found that blood ammonia levels were lowered and recovery seemed to follow in some cases. Bessman (20) noted that glutamate cannot cross the blood brain barrier and thus may act chiefly in the liver and muscle cells to fix the excess ammonia. The use of glutamate in hepatic coma has been advocated by a number of workers (2, 26, 29, 30, 31) but others have not been favorably impressed with its therapeutic value in this condition (14, 15, 19, 32). Roberts, Vanamee *et al* (26), who report success with glutamate, point out that the dosage must be adequate (at least 120 grams in 36-48 hours) to be effective in the acute case, and attribute failures reported by others in part at least to the use of inadequate dosage of the drug. There is general agreement on the importance of the following measures in the therapy of hepatic coma: (1) Withdrawal of precipitating factors; (2) Meticulous correction of electrolyte disturbances; (3) Prevention of endogenous ammonia formation in the colon by the administration of antibiotics, purging, and enemata; and (4) High carbohydrate intake.

In the case reported here, the above measures were vigorously applied. In a comment on this case, Dr. Sherlock (33) expressed the opinion that recovery would have resulted even without glutamate therapy. That of course may be true, and therefore the subtitle of this report states simply, "Recovery Following Treatment with Sodium Glutamate," drawing no conclusions as to cause and effect. However, in the light of this review, we plan to employ glutamate therapy should this complication of portacaval shunt occur in the future.

SUMMARY

A case is reported in which the patient recovered from coma occurring 12 days after a portacaval shunt for esophageal varices secondary to intrahepatic portal obstruction. Elevated blood ammonia, marked hypokalemia and alkalosis were the outstanding blood chemical abnormalities. Large doses of sodium glutamate and potassium salts were used in therapy.

The pathogenesis of the coma and the rationale of glutamate therapy is discussed.

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OBSERVATIONS ON THE NUCLEAR SEX CHROMATIN IN CRYPTORCHID TESTES.*†

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The demonstration by Barr and his associates (1-4) of sex differences in the nuclear structure of resting cells has been amply confirmed (5-8). Essentially, intermitotic nuclei of most tissues of females contain a conspicuous single mass of chromatin, the "sex chromatin". This body is approximately one micron in size and is usually planoconvex in shape with its flattened aspect in contact with the nuclear membrane. Staining intensely with hematoxylin, it is also Feulgen-positive. The sex chromatin is not affected by sex hormones (8). Indirect evidence indicates that this distinctive chromatin structure in females results from the fusion of portions of two X chromosomes (4). The absence of the sex-chromatin mass from cells of males is apparently due to the fact that the relatively small size of the Y chromosome produces an XY complex which is seldom larger than the remaining particulate chromatin material.

Sexual differences in nuclear morphology are customarily determined in skin biopsies (2), in oral smears (9, 10) or in circulating neutrophilic leucocytes (11). However, they may also be identified in the cells of various other tissues and organs, including those removed at necropsy (4, 7), in pathological material (12, 13) and in appropriate nuclei of the gonads themselves. Female nuclear morphology is present in nongametogenic cells in the normal ovary (4, 14) as well as in certain pathological tests (15-18).

Cytologic tests of chromosomal sex have provided a valuable and practical diagnostic aid in congenital errors of sex development (19). The accumulated experience of some of the principal investigators (19, 20, 18) in this field emphasizes the advisability of determining the chromosomal sex, as inferred from cytologic tests, in all instances of anomalous sexual development.

Although cryptorchidism is not ordinarily regarded as a congenital sexual aberration, the relatively high incidence of testicular dysgenesis in such testes (21) indicates the frequent presence of a congenital gonadal defect. Furthermore,

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cryptorchidism often accompanies pseudohermaphroditism and true hermaphroditism. In some of these conditions cryptogonadism may even be associated with a penile urethra (22, 23) in which case the true nature of the underlying sexual abnormality may be overlooked. In true hermaphroditism, where testicular and ovarian tissue are present simultaneously, the chromosomal sex in all extra-germinal tissues is either male *or* female, more frequently the latter (24, 19), indicating that the genetic or chromosomal sex may not always correspond with the nature of the gonads present. Indeed, in their first clinical paper, the Barr group (2) made just such a prediction.

The present study was conducted to investigate the chromosomal sex of a group of patients with cryptorchidism. A further stimulus in this work is the discordance between chromosomal and gonadal sex in certain patients with the Klinefelter-Reifenstein-Albright syndrome and in others with testicular dysgenesis (25, 17, 26-28, 15, 29, 16, 30, 18) as well as the discrepancy between chromosomal and genital sex in many patients with Turner's syndrome (31-33, 8). In the former group nuclear morphology of the female type may occur in patients with testes while male-type nuclear structure is common in the latter group of subjects with "ovarian agenesis" (gonadal dysgenesis). It was only by means of the expanding application of this type of sex detection that these highly significant observations were made.

The purpose of this report is to record the results of a detailed and systematic examination of the nuclear chromatin pattern in the cryptorchid testes of 59 patients. Chromatin-positive nuclei (the type found in females) were not encountered in any instance.

MATERIAL AND METHODS

Routinely prepared histologic sections were obtained from the cryptorchid testes of 59 patients ranging in age from two days to 78 years, with slightly more than one-half in the ten to 39 year age group. The age distribution is listed in Table I. Testicular tissue was procured at autopsy in three patients (aged two days, three and seven months). In the remainder it was obtained surgically by biopsy or ablation, most frequently during the repair of a hernia or at the time of orchiopexy. In two instances excision was performed because of involvement by a malignant tumor. The location of the undescended testicles was inguinal in approximately two-thirds and intra-abdominal in one-third of the cases.

The majority of the patients showed no evidence of constitutional or endocrine disease. Associated congenital anomalies were present in three infants whose testes were examined at necropsy (Table I.). Five individuals aged two months, 18 months, 13, 27 and 28 years were male pseudohermaphrodites. One of these, aged 13 years, had conspicuous shortness of stature while another, 27 years of age was a dwarf. Eunuchoidism due to prepuberal hypogonadism was present in a previously reported (34) 23 year old patient with rudimentary gonads.

Testicular specimens were fixed in ten per cent formalin in most instances. A

TABLE 1
Cryptorchid testes; age distribution of patients

Age	No. of Cases	Remarks
2 days to 18 months	6	2 male pseudohermaphrodites 3 (others) with multiple congenital anomalies
10 years to 14 years	13	1 male pseudohermaphrodite with shortness of stature
15 years to 19 years	8	
20 years to 29 years	11	2 male pseudohermaphrodites (one with dwarfism) 1 with prepuberal hypogonadism due to rudimentary gonads 2 with seminoma
30 years to 39 years	11	
40 years to 49 years	5	
50 years to 57 years	4	
78 years	1	
	59	

few biopsy specimens were fixed in Bouin's solution. All tissue was sectioned in paraffin, cut in thicknesses of six microns, stained with hematoxylin and eosin and examined under oil immersion.

The cells most suitable for examination of the sex-chromatin pattern are those with vesicular nuclei containing distinct chromatin granulation. The nuclei of Leydig cells, Sertoli cells and connective tissue cells meet these requirements while those of the germinal series of cells do not. Accordingly, the non-germinal cells of each testicular preparation were scrutinized. Although Leydig cells were not present in six specimens of the prepuberal age group, the nuclei of the undifferentiated cells and connective tissue cells in these sections were technically satisfactory. Some preparations of questionable technical quality were re-cut and re-stained so that nuclei of adequate technical quality containing fine structural detail were present in all of the histologic sections. Shrunken or degenerating nuclei, unsuitable for interpretation, were encountered in insignificant numbers.

RESULTS AND DISCUSSION

The over-all histopathology observed in the testicular tissue of these 59 patients was characteristic and conformed to the pattern previously reported (35) for 42 of these cases. Evidence of testicular dysgenesis (21) was observed in approximately one-half of the group beyond the prepuberal age. This indication of defective gonadogenesis was manifested principally by the presence of foci of immature or prepuberal-type seminiferous tubules.

In no instance were typical masses of sex chromatin observed. Skin biopsies were available in three patients and disclosed a male nuclear pattern. Some question may be raised concerning the technical quality of the testicular cells examined in as much as the sections were prepared in routine fashion employing

fixation with formaldehyde rather than with modified Davidson's solution (alcohol-formalin-acetic acid). However, the material forming the basis of this study was entirely satisfactory from a technical point of view, especially in the hands of those experienced with this type of microscopy. Moreover, testicular specimens prepared in the same manner yielded positive results in a previous study (17) in which characteristic sex-chromatin bodies were identified in the Leydig cell nuclei of certain patients with the Klinefelter-Reifenstein-Albright syndrome. Chromatin-positive nuclei have also been recognized by Plunkett and Barr (16) and by Nelson (18) in Leydig cells as well as in Sertoli cells of testicular biopsy specimens. Pertinent to the present study is the fact that the chromatin-positive testes of one of these patients (18) were also cryptorchid.

It is thus evident that under the conditions of this study, male-type nuclear morphology was present in all of the 59 patients. While this reaffirms the fact that a great majority of cryptorchid patients are chromosomal males, it should not be taken to preclude the occasional (and probably rare) instance of congenital error of sex development in which the chromosomal sex may be at variance with the gonadal sex. Continued investigations of this type will be necessary to disclose such anomalies.

SUMMARY

1. A study was conducted to investigate the chromosomal sex of 59 patients with cryptorchidism. The method employed was that based on the histologic test devised by Barr in which the nuclei of chromosomal females contain a characteristic mass of sex chromatin. Examinations were made of high-quality histologic preparations of cryptorchid testicular tissue.

2. Under the conditions of this investigation, male-type nuclear morphology was encountered in all instances.

3. The significance of these observations within the framework of congenital errors of sex development is discussed.

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THE DR. I. C. RUBIN LECTURES

THE FIRST LECTURE

SEYMOUR WIMPFHEIMER, M.D., CHAIRMAN

New York, N. Y.

The Rubin Lectureship has been established in honor of Dr. I. C. Rubin, in recognition of the many contributions he has made to gynecology and of his long years of service to The Mount Sinai Hospital. His work has earned him an important position among the leaders of his field and these lectures have been instituted to perpetuate his achievements. Dr. Rubin was born in New York City; he received his elementary and collegiate training in the schools of New York and his medical education at Columbia University. He served his internship at The Mount Sinai Hospital where he has risen eventually to his present rank of Consulting Gynecologist and where he has practiced his specialty for more than fifty years.

Dr. Rubin has received many honors, too many to enumerate at this time. Among the major awards he has received are an honorary degree from the University of Athens in 1952; and an honorary degree from the University of Paris in 1955. He is an officer of the Legion of Honor. He is an honorary member of many gynecological societies throughout the world. He has held official positions in many of these societies. He was recently President of the American Gynecological Society. He has written over 130 papers, several books and only recently, in association with Dr. Novak, a three volume monograph on "Integrated Gynecology". His interests have been broad and include numerous subjects in gynecology and obstetrics. The field of sterility has occupied a great deal of his attention. His pioneer and monumental research in this specialty establishes him as its leader.

INTRODUCTION

ELI MOSCHCOWITZ, M.D.

New York, N. Y.

I am sure many of you share one of my day dreams, namely, the longing to have communion with some of the great minds of the past; those who have moulded the world's thoughts, who have stirred our emotions and made this world healthier than it was before. In literature, what would one not give to have conversed with Shakespeare, Sam Johnson or Moliere; in music with Beethoven or Mozart or Schubert, and in science, Newton or Harvey and above all Louis Pasteur. I have selected these not because they are my favorites but because there is something Olympian in their stature that inspires reverence and because their impact on the minds of men is everlasting.

Tonight we shall come close to a realization of at least one of these dreams

Given at The Mount Sinai Hospital, New York, N. Y.

because you will meet Prof. Vallery-Radot, one in whose veins runs the blood of the greatest scientists of all times, Louis Pasteur.

In passing may I be permitted to comment on one of the ironies of fame. In Paris millions visit the tomb of Napoleon Bonaparte who killed millions while only a handful visit the modest tomb of Louis Pasteur who saved the lives of many millions.

But Dr. Vallery-Radot was not invited to give this lecture merely because he is the grandson of Louis Pasteur. He is a distinguished person in his own right. He has done fundamental work in the fields of anaphylaxis, and renal disorders. He is Clinical Professor of Medicine in the faculty of Medicine of Paris and Director of Medicine in the Broussais Hospital and it was under his direction that the antihistamine drugs were first introduced. He is President of the Board of Directors of the Pasteur Institute.

Dr. Vallery-Radot is distinguished in many *ex cathedra* activities. He has been French ambassador to Brazil and he has the unique distinction of having sat in the French Senate as well as in the National Assembly. He is also a member of the French Academy. This is one of the highest honors that can be given to a Frenchman. The membership is limited to 40 and comprises the elite of the French literary world. In this respect he follows the footsteps of his grandfather. Incidentally, Louis Pasteur's speech of acceptance when he was inducted is a magnificent statement of his credo of science, and deserves more widespread recognition. One of Dr. Vallery-Radot's many labors is the publication of his grandfather's writings.

Ladies and gentlemen, I have the honor to present Professor Pasteur Vallery-Radot who will speak on the relation of allergy to gynecology.

ALLERGIC MANIFESTATIONS OF THE FEMALE PATIENT FROM PUBERTY TO MENOPAUSE

PASTEUR VALLERY-RADOT, M.D.*

Paris, France

Mr. Chairman, Colleagues, Ladies and Gentlemen:

I thank the Committee of The Mount Sinai Hospital in charge of the Dr. I. C. Rubin Lectures for the great honor they have accorded me by the invitation to give the first lecture in honor of Dr. Rubin at The Mount Sinai Hospital, where his work was so brilliantly done during many years.

May I tell you what we think of Dr. Rubin in Europe? He is deservedly considered as the best gynecologist in the world. Not only is he greatly admired,

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but he also enjoys the affection of all who know him. He is highly esteemed and loved for his exceptional kindness, his well-known courtesy, and for the absolute trust his patients place in him. He epitomizes, not only the qualities of a great physician, but also those of a great-hearted man.

It was difficult for me to choose a subject. Not being a gynecologist, I could not talk of gynecology, and yet, from this Chair it would be difficult not to do so. I tried to avoid this obstacle and proposed to the Committee, Allergic Manifestations of the Female Patient from Puberty to Menopause. They very kindly accepted this.

It seems to me that if one wants to make clear this subject, it is necessary to distinguish the allergic symptoms such as asthma, spasmodic rhinitis, urticaria, angioneurotic edema *influenced* by the different stages of a woman's life between puberty and menopause, from the allergic symptoms *due to* hypersensitivity to ovarian hormones.

ALLERGIC SYMPTOMS INFLUENCED BY DIFFERENT STAGES OF THE HORMONAL LIFE OF A WOMAN

It is generally admitted that certain forms of children's asthma suddenly disappear at the age of puberty. One knows that, when puberty starts, the estrogens are actively induced, and that the hypophysis is responsible for such hormonal activity. The gonadotropic hormone appears in the urine, the excretion rate of estrogens sharply decreases, while the excretion of androgen rises only slightly. It is just when this hormonal change takes place that infantile asthma sometimes disappears. But the fact is not quite as frequent as ancient authors maintained.

It is frequent to observe, after puberty, generally two or three days before the menses, an increase of the allergic symptoms such as asthma, angioneurotic edema, migraine—whether the menstrual period is normal or abnormal. Turiaf, Blanchon and Zizine (1) found, in eighty-three cases of asthma influenced by the menstrual cycle, seventeen cases where the cycle was regular; the other sixty-six cases representing some irregularity in the menstrual cycle. When menstruation was normal, the hormonal treatment (with estrogens or progesterone) aggravated the asthma. On the contrary, the other sixty-six patients were improved by the same treatment and, in some cases, complete relief was achieved. Among four hundred and thirty-three women suffering from asthma, that we recently studied, we found twenty-one cases of asthma influenced by the menstrual cycle. The symptoms of asthma increased during the two or three days preceeding the menses. It is well known that the rate of folliculinemia reaches its maximum before the menses and suddenly falls afterwards. The allergic symptoms may possibly be ascribed to this hyperfolliculinism, but that is not certain.

During *pregnancy*, while the rate of estrogens and of progesterone is getting higher and the body is filled with gonadotropic hormones of pituitary and placental origin, it is very frequent to observe a great relief or even the disappearance of asthma, migraine or other allergic symptoms. This usually happens

during the third or fourth month of pregnancy. Some women, suffering from migraine or asthma know that they are pregnant by the disappearance of their headache or asthmatic crisis. In our own statistics concerning four hundred and thirty-three asthmatic women, we found seven cases in which asthma disappeared during pregnancy, four cases in which asthmatic crises were persistent but less frequent and less severe. Unfortunately, we did not note how many women out of the four hundred and thirty-three cases had been pregnant, nor did we note if an asthmatic woman was relieved of her asthma every time she was pregnant.

This disappearance of asthma or other allergic manifestations during pregnancy may be compared with some experimental facts. Duran Reynals (2) and later Lumière and Couturier (3) showed that female guinea-pigs, sensitized before fertilization, became refractory to anaphylactic shock during gestation. After the delivery, the state of sensitization reappeared. Asthma or migraine generally reappears soon after delivery. Zondek and Bromberg (4) held the opinion that this improvement in the asthmatic state might be explained by the fact that the gradual increase of the hormonal rate of the body during pregnancy could create a sort of hormonal desensitization. This supposition has not been proved.

Ahlmark (5) and later Werle and Schmidt-Elmendorf (6) supported the belief that during pregnancy the amount of histaminase in blood plasma was very high while histaminase can barely be found in the plasma of a non-pregnant woman. This enzyme is produced by the placenta. Is the hyperhistaminase the explanation of the disappearance of asthma during pregnancy? The author affirms this because in the cases where there is no improvement of asthma during pregnancy, the rate of histaminase in the blood is much lower than in other pregnant women. This has not been confirmed.

Another hypothesis that has been put forward is that after the third month of pregnancy there is a production of ACTH by the placenta. None of these views seem to us worth retaining because very often the allergic symptoms, particularly asthma, are aggravated instead of being relieved by the state of pregnancy, as Vignes, Green, Zizine observed (7-9). In his observations of thirty-two cases of asthma, Zizine (9) notes an increase in the symptoms in thirteen women. Turiaf (1) observing one hundred and forty-one pregnant women, found aggravation of the asthmatic state in eleven cases and improvement in thirteen cases. As we shall see later, asthma sometimes appears for the first time in the course of pregnancy.

At the time of *menopause*, asthma may disappear, or on the contrary, appear (10-12).

From all these discrepant facts, it seems difficult to conclude that one hormone or another favors or hinders the allergic manifestations. Moreover, good results are obtained with opposite treatments; sometimes with folliculin, sometimes with progesterone. In the actual state of our knowledge, Claude, Allemany Yall (13) and I think that, as there is a close relation between the hormonal and the nervous system, any important change in the hormones reacts on the neurovegetative system and affects also the allergic manifestations which are partly connected with the neurovegetative system.

THE ALLERGIC MANIFESTATIONS DUE TO A SENSITIZATION TO
OVARIAN HORMONES

Allergic symptoms, such as urticaria, angioneurotic edema, herpes, dermatitis, pruritis valvae, asthma, spasmodic rhinitis, migraine, fever, may be observed only in the menstrual or premenstrual period. Sometimes, but not always, migraine, asthma or other allergic manifestations appear only at puberty. A typical case report was given by Widal, Abrami and de Gennes (14) in 1922, of a woman who had suffered from an attack of asthma for the first time when the menses appeared at the age of fourteen; asthma disappeared when she became pregnant, reappeared with the menses and disappeared again at the time of menopause. Our own records of four hundred and thirty-three asthmatic women showed five cases of asthma solely premenstrual with hyperfolliculinemia proved by the examination of vaginal smears. Hormonal treatment gave good results.

In 1935, our collaborator, Carlo Alice (15) had published twelve case reports collected in our Clinic in which asthma occurred in relation to the menstrual period. Injections of Corpus luteum extracts gave excellent results in the majority of cases.

The first interesting study on hypersensitivity to hormonal substances is that of J. Geber in 1921 (16). He observed that premenstrual urticaria could be induced during the intermenstrual period by the injection into the patient of her own serum, collected just before the menses. Geber also observed that premenstrual urticaria could be prevented by systematic injections of blood-serum collected in the premenstrual period; he practiced in this as a sort of desensitization. These facts were confirmed by several other workers including Lichter, Malinin, Harrison, Salen, Hopkins and Kesten, Urbach, Waldbott (17-33) from 1924 to 1941.

In 1942, Urbach (24) ascribed the premenstrual allergic symptoms to ovarian allergy; however, it is the work of Zondek and Bromberg (25) in 1945 that gave definitive proof of this auto-allergy. They showed that, in certain cases, treatment with injections of esterone or estradiol were followed by allergic symptoms such as urticaria. On the other hand, they observed that the repeated injections of small doses of estrogenic hormones gave relief through desensitization to women presenting premenstrual urticaria. They carried out intracutaneous tests with the following hormones: estradiol, esterone, progesterone, pregnandiol, testosterone, androsterone, dioxycorticosterone acetate—all of these hormones being in oil. The patients tested presented an allergic manifestation during the premenstrual period. Among one hundred and sixty-five patients (tested during the premenstrual period) a positive reaction was obtained in 70 per cent of the cases, the reaction appearing within twenty-four to forty-eight hours. The normal patients had no reaction. These authors made another remarkable statement: the blood-serum of a woman presenting a premenstrual allergic manifestation, was collected just before the menses. This serum was injected in the skin of a normal woman in the premenstrual period; a local reaction appeared. The serum taken in the intramenstrual period had no action. It was a real, spontaneous Prausnitz-Küstner reaction. This very remarkable experiment was success-

fully repeated many times. Desensitization practiced on forty-four patients gave excellent results in twenty-two cases and quite satisfactory relief in twelve cases.

The hypersensitivity to endogenous hormones, proved by Zondek, was confirmed by many authors. We shall mention the most important reports.

In 1947, Biozzi (26) related four cases of menstrual symptoms, thoroughly examined. He found positive intradermal tests to estradiol and also positive Prausnitz-Küstner reactions. In two cases he obtained a complete desensitization. The same year, Hartmann (27, 28) published similar case reports of sensitization to estradiol.

In 1948, an important study was published by Baer, Witten and Allen (29). Observing one hundred and twenty-two patients presenting skin troubles, these authors showed that in thirty-eight cases connected with menstruation or menopause, four intradermal reactions were positive to steroid hormones. In sixty-four cases of dermatitis without any relation to the hormonal function, all the skin tests were negative.

In 1949, Phillips (30) referred to a case of positive skin test to pituitary gonadotropin with good results of a desensitization treatment.

In 1950, de Wit (31), studying sixty cases of migraine, found in thirty-nine cases a positive intradermal reaction to estradiol or esterone.

In 1951, Heckel reported cases in which 85 per cent of positive tests to hormones in premenstrual headaches were described (32). The same year, Solari, Moreno and Fernandez published another record (33) and Biozzi his essay (34). This author studied one hundred and thirty-three women presenting a premenstrual allergic symptom. He obtained positive intradermal tests in 20.5 per cent of the cases with estradiol or esterone or progesterone or testosterone, or with a few of these hormones. The classical P.K. reaction was positive in 22 per cent of the cases with serum collected in the premenstrual period and in 11 per cent of the cases tested with the serum collected after the menses. The spontaneous P.K. reaction, such as we described it before, was positive in 33 per cent of the cases tested with the premenstrual serum and in 22 per cent of the cases tested with the post-menstrual serum. The allergic symptoms were induced in 53 per cent of the cases by injecting the appropriate hormone.

In 1953, Cazzola reported (35) at the Forty-third Italian Congress of Obstetrics and Gynecology, confirming these facts, and in the same year, a study by Heckel (36) in which he admits pregnandiol to be the principal hormonal antigenic agent.

In 1954 another interesting paper appeared from two Swiss workers, Aeppli and Herzmann, (37) showing that menstrual herpes is in relation with hypersensitivity to progesterone and may be efficiently treated by ovocycline.

In all these reports, we find the proof of an autosensitization to a steroid hormone: oestrone or oestradiol or progesterone or testosterone, sometimes to many of them or all. Much more seldom, the sensitization is due to pregnandiol or to gonadotrophin. Evidence of sensitization is given by intradermal tests, the spontaneous P.K. reaction, the P.K. reaction practiced in the classical way, and lastly by the efficiency of the desensitization treatment.

Amongst the most recent works, we shall specially mention two of them: one is a Swedish work by Tore Wahlen, (38) the other an Italian work by Malizia (39).

Tore Wahlen relates the cases of women, between eighteen and forty-five years of age, presenting severe menstrual or premenstrual symptoms. The steroid hormones used for the intradermal tests were prepared by the following method: each separate hormone was added to the patient's serum, the mixture was kept for twenty-four hours in the incubator at 37°C, and during this time repeatedly shaken. In thirty-five cases tested, Tore Wahlen obtained twenty-nine positive reactions, fifteen to estrogens, six to progesterone, five to testosterone, three to the different hormones. Partial or complete desensitization was achieved by repeated injections of the responsible hormone in 73 per cent of the cases.

Malizia (39) reports having practiced intradermal reactions on two hundred and twenty-one women presenting allergic premenstrual or menstrual symptoms. He employed the different hormones either in oil-solution or in aqueous suspension of microcrystals. The hormones employed were: estradiol, estrone, progesterone and testosterone. He obtained a positive reaction in 22 per cent of the cases to one or many hormones. The reaction appeared within six to forty-eight hours after the injection. The small number of positive reactions obtained is not at all surprising, as he tested not only women presenting allergic menstrual troubles, but also women presenting allergic symptoms aggravated during the menstrual period. As we previously remarked, hormonal allergy concerns only allergic symptoms *provoked by* menstruation, and does not include allergic manifestations *influenced by* menstruation; these symptoms were described in the preceding chapter.

Malizia practiced the classic transfer of passive sensitization: the P.K. reaction. The positive reactions appeared within an hour.

The same author also obtained a spontaneous transfer of sensitization by injecting to a normal woman during the premenstrual period the serum, taken from an allergic woman during the premenstrual period. The positive reaction was obtained within six to twenty-four hours.

The hormonal allergy we are studying is an auto-allergy. It might be interesting to compare these cases with some allergic manifestations observed in the course of hormonal therapy. In that occurrence we have an exo-allergy.

Zondek, as already stated (25), observed allergic manifestations in women who had been treated with follicular hormones. Harten and Walzer (40), Waldbott (23), Loftis (41), Mitchell (42) observed similar cases.

Serafini and Malizia (43) recently reported three remarkable cases: two of them were cases of sensitization to progesterone, one was a sensitization to estradiol. In the first case, after the fourth injection with 25 mgm. of progesterone, a wide spread urticaria appeared. In the second case, the second injection with progesterone was followed by urticaria and Quincke's edema. In the third instance, on the fourteenth day of treatment with ovocycline, the injections being practiced every three days, the patient felt a general uneasiness and a swelling of the face. The next injection, on the eighteenth day, induced Quincke's edema of the face.

This allergic symptom appearing after treatment was reproduced during each

menstrual period. Intradermal tests, P.K. reaction, spontaneous transfer of sensitization, were positive. Desensitization therapy achieved the disappearance of the premenstrual symptoms in the three cases. These three cases show the possibility of an allergy induced by injected hormones becoming an auto-allergy to the same hormones.

In a very recent work of July 1955, Heckel (44) showed that rabbits and guinea-pigs could be sensitized to pregnandiol.

So, the steroid hormones may become allergens, and yet one might object that the steroid hormones are not antigenic. But we do know, since Landsteiner's famous work, that haptens combined with the proteins of the organisms form antibodies. The steroids may be considered as haptens. This is furthermore demonstrated by the work of Brandt and Goldhammer (45): these authors showed that steroid hormones, joined with a protein and injected in the body, may bring about the production of specific antibodies.

The possibility of a sensitization to sex-hormones can now be asserted. It seems however that there is no parallelism between the degree of sensitization and the rate of the hormones. Herschberg (46) compared the results of intradermal tests with the level of hormonal activity, revealed by the examination of the vaginal smears or by the endometrial biopsy: thirteen per cent of the women presenting a positive intradermal reaction to estrone had also hyperfolliculinemia, eighty-seven per cent presented a normal rate or even hypofolliculinemia.

In the case of allergy appearing only in the menstrual period, we have seen that hormonal sensitization must be searched out and that the antigenic hormone varies. To detect this auto-allergy, it is necessary to use a test-method that leaves no doubt. Unfortunately the methods employed change with the different authors, and either allergy fails to be proved or else is affirmed without certainty.

Here are the principal rules to be followed:

Hormonal antigens were generally used *in oil*: in olive oil, peanut oil, sesame oil, sweet-almond oil. These oils, before being mixed with the hormones, are kept a few days at a low temperature (zero to five degrees centigrade). They must be strictly neutral or else they may produce false reactions. They also may contain fatty acids and these can also give false reactions. Furthermore, some patients present an oil-allergy (Solari, Moreno (33)). As you see, there are many possible causes for errors.

If oil is employed, it is necessary to effect a great number of control-tests on the patient tested and on normal women.

The intradermal tests are practiced with a solution of one mg of hormone in 1 cc of oil. The dose injected is one tenth of a cc. The reaction is of the delayed-type and appears within the third and twelfth hour, sometimes even later, the apex being generally around the twenty-fourth hour. The reaction is of the edematous inflammatory type.

We have already described Tore Wahlen's technique. *The hormones are dissolved in the patient's serum.* The mixture is kept for twenty-four hours in the

thermostat and repeatedly shaken. We shall not insist on this method, as we do not think it has been used by any one else.

Aqueous solutions containing one tenth or one hundredth of hormone per cc have been used; one tenth of a cc is injected. The reaction is in this case of the immediate type, appearing in twenty to thirty minutes.

These aqueous solutions are obtainable only with estrone. For the other steroids, it is necessary to add a solvent such as sodium oleate or glycolate, and the solvent may be irritating to the skin.

Microcrystals in aqueous suspension are more advisable. Zondek and Bromberg, Heckel employed this method. They first employed the oil solution as it was then difficult to get microcrystals. But all their recent work as well as Malizia's was realised with microcrystals in solution.

We think the best way is to prepare three solutions: one containing 1 mg of microcrystals per cc.; the second, one tenth of a mg per cc.; the third one hundredth of a mg. Intradermal injections of one tenth of a cc. are practiced. The reaction is of the delayed-type as the reaction observed with an oil-solution injection. But the apex appears earlier. In some cases, the reaction is of the immediate type.

In current practice, the intradermal reactions are made with the following hormones: estrone, estradiol, progesterone, and testosterone; control-tests are effected with other steroids having no sex activity and prepared by the same method.

AT WHAT TIME, DURING THE MENSTRUAL CYCLE SHOULD THE PATIENTS BE TESTED?

Positive intradermal reactions can be obtained at any moment during the menstrual cycle, but it seems that it is during the premenstrual period that the intradermal reactions are most definite. The premenstrual period is then the best time to practice the reactions. In one case we have seen the intradermal injection of folliculin, effected during the intermenstrual period, becoming positive eight days after the injection, during the menses.

The results of the intradermal reactions must be confirmed by means of the classical P.K. reaction. The patient's blood is taken during the premenstrual period; one tenth of a cc. of the serum is injected in the skin of a normal woman. Twenty-four hours later, exactly in the same spot one tenth of a cc. of a solution of 1 mg of hormone (aqueous suspension of microcrystals), is injected. The reaction appears, within half an hour to an hour, after the injection. Control-tests must of course be made.

The passive spontaneous transfer of hypersensitivity may also be ascertained: one tenth of cc. of serum of the patient, taken during the premenstrual period, is injected to a normal woman during her premenstrual period. A local reaction starts after six to twelve hours. Twenty-four hours after the reaction is definitely positive, and as intense as a classical P.K. reaction. Sometimes the reaction appears much earlier. A control-test must be made with the serum of a normal woman.

One should also try to *reproduce, during the intermenstrual period, the symptoms observed during the menstrual or premenstrual period*. The hormones tested are injected to the patient during the intermenstrual period, and the allergic symptoms generally observed during the menstrual period appear a few hours after the injection. After all these tests, the *specific desensitization treatment* still remains to be tried.

Standard oil solution may be used. In the case of sensitization to oestradiol: ovocycline; in the case of sensitization to progesterone: lutocycline.

At the beginning of the treatment, very small doses should be given, according to the results of the intradermal reactions. Daily injections are made during the first sixteen days of the menstrual cycle, beginning immediately the first day of the menses. Doses should be progressively increased, according to the patient's reactions. This desensitization treatment should be continued for many months. In quite a few cases, very good results are obtained.

These are all the tests that should be practiced to detect allergy to ovarian hormones. Failing this rigorous method, it is impossible to assert the auto-allergy to sex-hormones.

ALLERGIC SYMPTOMS PROVOKED BY PREGNANCY

It is very unusual for asthma to appear with the state of pregnancy and to disappear just after the delivery.

We observed such a case with Carlo Alice (15): a woman had her first asthmatic crisis at the age of twenty-seven and in the sixth month of pregnancy. After delivery, asthma disappeared, but in the second month of another gestation she had again very severe asthmatic crisis. After delivery, she was free of asthma until the fourth month of the next pregnancy.

Hyde Salter (47) in 1860, Audebert (48) in 1900, had already related cases of asthma appearing only during pregnancy and ceasing with delivery. Other report-cases were published by Chambrelent and Cathala (49), Schpolianski (50), Fornero (51).

Itching and skin manifestations appearing in the course of pregnancy are quite frequent. They have been related to a fetal or placental sensitization. The fetus and the placenta, acting perhaps as antigens, provoked the formation of antibodies in the gravid organism. Rosenau and Anderson (52) showed that guinea-pig could be sensitized to guinea pig's placental extract.

Urbach (53) realized a remarkable experiment: he practiced intradermal reactions with 0.1 cc. of fetal extract (the fetus employed for this extract was six to eight weeks old). Women in a state of pregnancy for a few months presented a strong reaction within twenty-four hours; on the contrary, women in the last month of their pregnancy presented only a very slight reaction or even no reaction at all. Urbach concludes that the maternal organism becomes sensitized to the fetal proteins, and after a few months a specific inactivity towards the same proteins is acquired. It is possible to think that itching the skin troubles, as well as nausea and vomiting, so often observed in the early state of pregnancy, are perhaps due to an allergy to the fetus. The cutaneous injections of 10 cc. of

serum taken from normal pregnant women, practiced twice a week, might relieve pregnant women presenting such symptoms.

One might wonder if eclampsia might not be in relation with a fetal or placental sensitization. Yamada (54) showed that the isolated uterus of a guinea-pig, sensitized with the serum of an eclamptic woman, contracts *in vitro* by the addition of placental proteins. Junghans (55) showed that women in a state of pre-eclampsia had strong intradermal reactions to fetal extracts.

Other suggestive researches have been carried out. Lévy-Solal and Tzanek (56, 57) showed that the guinea-pig, after being injected with the serum of an eclamptic woman, presents manifestations of the anaphylactic shock type. This experiment has not been reproduced but, anyhow, it only proves the toxicity of the eclamptic serum. These experiments are lacking confirmation, but it should be very interesting to prove that eclampsia is due to a sensitization.

ALLERGIC SYMPTOMS APPEARING AT THE AGE OF MENOPAUSE

Some women who never suffered from asthma start having asthma at the time of menopause.

Out of four hundred and thirty-three asthmatic women that we studied, asthma appeared during the menopause in six cases, very shortly after the disappearance of the menses. Hormonal treatment brought a great relief.

Maurice Dérot and Robert Tricot (58) reported an interesting case of asthma appearing after a total hysterectomy.

In many cases, asthma seems to appear with menopause, but on examining closely the case-histories, one finds that light crisis of asthma or spasmodic rhinitis or spasmodic cough occurred previously. The symptom observed was not really due to menopause. What we have just said about asthma may be applied to migraine.

Jimenez Diaz (11) thinks that hyperfolliculinemia is the cause of menopausal asthma, because folliculine has a vagotonic action. To this view we can oppose the fact that it is sometimes oestrogen treatment or sometimes progesterone treatment that brings relief. This menopausal asthma seems due to the profound humoral changes occurring during this period of a woman's life. Nothing more can be ascertained.

This study shows how much allergy crosses the field of gynecology as it crosses other fields of medical practice.

Every gynecologist should think about allergy. But there are yet many unknown chapters, and it would be a mistake to ascribe systematically to hormonal interference allergic symptoms with no definite cause. Wisdom and scepticism must always be the rule of the physician. He must yield only to well established facts.

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PROLONGED APNEA FOLLOWING THE USE OF SUCCINYL- CHOLINE IN ANESTHESIA: A CASE REPORT

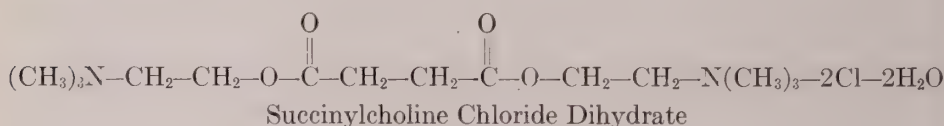
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Succinylcholine (or diacetylcholine) is a synthetic drug produced by linking two molecules of acetylcholine together at the alpha methyl group in such a manner that there are ten atoms interposed between the two quaternary nitrogen atoms; this structural feature is hypothesized as necessary for its neuromuscular blocking activity (1-5).



Succinylcholine was first studied and synthesized by Hunt and Taveau in 1906 and 1911 (6, 7). Its pharmacological properties and potent neuromuscular blocking activity have only recently been described (8-12). It has been utilized and investigated clinically by Foldes and others (13-16).

The dichloride is a white solid which crystallizes with two molecules of water. The dehydrate so formed has a melting point of 157°C and is readily soluble in water to form a stable acidic solution (1, 17). It is rapidly hydrolyzed by alkaline solutions.

Succinylcholine belongs to the "depolarizing" group of neuromuscular blocking agents. It produces persistent depolarization at the postjunctional membrane of the neuromuscular endplate (18). In this manner, succinylcholine prevents the physiological depolarization-repolarization sequence caused by the acetylcholine-acetylcholinesterase system that is essential for normal neuromuscular transmission (18). Tubocurarine, on the other hand, produces muscle paralysis by inhibiting the normal depolarizing by acetylcholine ("persistent polarization").

Succinylcholine is hydrolyzed primarily by "pseudo" or plasma cholinesterase and, to a lesser extent, by true acetylcholinesterase (20-26). Hydrolysis of succinylcholine is a two stage process. There is first a rapid production of succinylmonocholine and choline; this is followed by a slower hydrolysis of succinylmonocholine to succinic acid and choline (27). Succinylmonocholine possesses a neuromuscular blocking effect with slower onset and longer duration of action than the dicholine (28-30). The hydrolysis of succinylcholine is inhibited by neostigmine and other anticholinesterase drugs.

The clinical effects of intravenous succinylcholine are rapid in onset, brief, intense and reproducible. Muscular fasciculations, which may follow the rapid

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intravenous administration of succinylcholine, can be obviated by a slow injection and are followed by muscular paralysis and relaxations. Muscle paralysis will persist for one to four minutes after which the patient is in the pre-injection stage. Apnea may occur simultaneously with the muscle paralysis, depending upon the dose given. Unlike tubocurarine, succinylcholine produces neither a histamine release nor a blockade of the autonomic ganglia in dosages clinically used.

Recent literature documents many cases of prolonged apnea following succinylcholine (31-41). Very few cases, however, were as severe and prolonged as the case to be reported, a case in which there was apnea of six hours' duration, followed by inadequate respiration for 10 hours and respiratory difficulty for the next 24 hours.

CASE REPORT

A 51 year old white male was admitted to The Mount Sinai Hospital on June 5, 1954 with complaints of marked weakness, nausea, hematemesis and melena. These symptoms appeared on the morning of admission.

The patient had had encephalitis lethargica at the age of 29 years; there were sequelae of slurring of speech, occasional muscle twitching and some impairment of memory for recent events. He was known to have hypertensive cardiovascular disease for several years; one week before admission he was digitalized and given mercurhydrin because of acute congestive heart failure. There was no history of gastrointestinal disturbances.

On physical examination his temperature was 98.8°F, pulse 104 per minute, respirations 30 per minute and blood pressure 100/75. He appeared pale, sweaty and apprehensive. The heart was enlarged; systolic murmurs were heard over the apex and pulmonic area. The abdomen was soft and not tender. Examination of the urine was negative. The hemoglobin was 14 gram per cent and the white blood count was 13,600 per cu. mm. Guaiac test of the stool gave a four plus reaction.

Active gastrointestinal bleeding continued for 24 hours following admission. He received six units of stored whole blood and five units of packed red cells during that period. Because of continuing, active gastrointestinal bleeding, it was decided to perform an exploratory laparotomy.

Pre anesthetic medication consisted of Demerol (100 mg.) and atropine sulfate (0.4 mg), given at 3 P.M., June 6, 1954. The patient arrived in the operating room at 3:45 P.M.; at that time the blood pressure was 90/40 and respirations were shallow. Anesthesia was begun at 3:55 P.M.; cyclopropane was used with a circle carbon dioxide absorption technique. In order to permit oral endotracheal intubation, 40 mg. of succinylcholine was given intravenously at 4 P.M.; intubation was prompt and uneventful. The apnea following the administration of succinylcholine necessitated controlled respiration.

The operation was begun at 4:10 P.M. and was completed at 6:45 P.M. A subtotal gastrectomy for a large prepyloric ulcer was uneventfully performed. During the operation 1500 cc. of blood was administered; the blood pressure ranged from 95/55 to 130/65. An intravenous infusion of 0.1 per cent succinylcholine was begun at 4:15 P.M. and continued intermittently throughout the operation; this insured adequate muscle relaxation in light cyclopropane anesthesia. A total of 440 mg. of succinylcholine was utilized. Controlled respiration was performed during the full course of the operation.

The patient remained apneic after termination of the operation. Artificial respiration with the anesthetic machine was continued. At 7:30 P.M., nalorphine (5 mg.) was given intravenously without effect. The patient's blood pressure and pulse rate continued at satisfactory levels; the general appearance of the patient remained good. At 9:17 P.M., 4.5 cc. of Metrazol were administered intravenously in divided doses; the patient responded

to this with a definite increase in general muscle tone. At 10 P.M. the patient responded to painful stimuli, e.g. supraorbital pressure, with an occasional short, jerky breath. Spontaneous respirations appeared at 10:45 P.M. These respirations, however, were short, spasmodic and inadequate, necessitating the continuance of mechanical assistance to respiration.

At 1:30 A.M., June 7th, the blood pressure fell suddenly to 70 systolic. A continuous slow infusion of norepinephrine (8 mgm. per 1000 cc. solution) was begun promptly with a return of blood pressure to 110/60. The patient was placed in a tank type respirator at 2 A.M. because of continuing inadequate respiratory efforts; oxygen was administered by insufflation through the endotracheal tube. At 2:30 A.M., the patient awakened and appeared alert and answered questions by movements of his head and hands. The patient was removed from the respirator, but was returned to it promptly because of respiratory distress. The endotracheal tube was removed at 8 A.M.

During the following 24 hours, the patient's condition was satisfactory. Blood pressure and pulse were within normal limits. The tank type respirator was used for progressively shorter intervals. On the morning of June 8th there was no further need of the respirator. Both circulation and respiration were adequate during the remainder of the day.

At 7 P.M., June 8th, the patient became cyanotic and hypotensive. This clinical picture persisted in spite of the administration of a dilute norepinephrine infusion, intravenous adrenal cortical extract and 100 per cent oxygen. There was progressive deterioration in the patient's condition until expiration at 1 A.M., June 9th.

Post mortem examination revealed reactive peritonitis, hypertrophy of the heart with marked hypertrophy of the right ventricle, marked arteriosclerosis of the pulmonary arteries, atelectasis, congestion, edema and emphysema of the lungs, and multiple, small pulmonary emboli without infarction.

DISCUSSION

Several theories have been offered to explain prolonged apnea following the use of succinylcholine. Foldes (42) has succinctly listed them as follows:

1. Low plasma cholinesterase levels.
2. Accumulation of succinylmonocholine; this is most apt to occur when low plasma cholinesterase activity is combined with an oliguria.
3. Central respiratory depression by succinylcholine.
4. Central respiratory depression by general anesthetic agents.
5. Altered response of the neuromuscular endplate to succinylcholine; it is suggested that under unusual conditions succinylcholine may produce a prolonged non-depolarizing block rather than its usual depolarizing effect.
6. Failure of redistribution of succinylcholine from the neuromuscular endplate.
7. Persistent changes after removal of succinylcholine from the endplate (refractory muscle).
8. Controlled respiration with resulting hypercapnia, apnea, exhaustion of the Hering-Breuer reflex or interference with the reflex regulation of the respiratory center.

We can only speculate as to which factor, or combination of factors, was responsible for the prolonged apnea in this patient. It appears most probable that the important etiological factors in our case were the following:

1. Low plasma cholinesterase levels.
2. Central respiratory depression by premedicant drugs, anesthetic agents and succinylcholine.

3. Prolonged passive hyperventilation with exhaustion of the Hering-Breuer reflex and lowering of arterial carbon dioxide below levels necessary for stimulation of the respiratory centers.

Evans et al (21) and Foldes (43) have shown that a causal relationship exists between prolonged apnea and respiratory depression, and the use of succinylcholine in patients with low plasma cholinesterase. Diminished plasma cholinesterase is seen in anemia, liver disease, malnutrition and cachexia. Our patient may well have had markedly lowered plasma cholinesterase because of his severe, protracted hemorrhage and the use of massive transfusions of stored, whole blood. Unfortunately, a blood sample taken for cholinesterase determination was lost.

The possibility that central respiratory depression played a significant role in this patient is suggested by the observation that painful stimuli (e.g. supraorbital pressure) produced short, jerky respiratory movements well before the return of spontaneous breathing. Central respiratory depression follows frequently the use of cyclopropane and narcotic analgesics. If to these effects, we add those of prolonged controlled respiration with hypercapnia or apnea and exhaustion of the Hering-Breuer reflexes, an altered physiologic state exists favorable to the production of prolonged apnea.

A recent paper by Irwin et al (44) suggests still another etiological factor in this case. The workers showed that succinylcholine apnea is significantly prolonged when the level of blood calcium ion is lowered. Our patient received 7.5 liters of stored blood prior to and during the operation. It is conceivable that the large amounts of citrate accompanying these transfusions depressed the blood calcium ion levels sufficiently to prolong the effect of succinylcholine. Another point of interest is the fact that the calcium ion antagonizes neuromuscular blocking agents like d-tubocurarine (45). If it is true that the succinylcholine block resembles that of d-tubocurarine, except for its early phase of action, then a diminished calcium ion level may enhance the neuromuscular block of succinylcholine. These suggestions are purely speculative, but merit presentation.

A bizarre aspect of this case was the prolonged period of inadequate respiration necessitating the use of mechanical assistance. The clinical picture, during this interval, was typically one of partial curarization. Respirations were short and jerky, shallow and diaphragmatic in nature. With clinical improvement, there was a gradual, but steady, return of intercostal breathing, a decrease in respiratory rate and an increase in tidal volume. There was no evidence of massive atelectasis, pneumothorax or pulmonary edema. It is difficult to explain this prolonged bout of respiratory difficulty. One is forced to speculate that, for reasons unknown, a remarkably long neuromuscular block occurred.

The cause of death in this patient could not be determined anatomically. No single pathologic change was of sufficient and obvious severity to account fully for death. One is forced to the conclusion that death was the result of a summation of morbid factors, primarily marked cardiac hypertrophy, atelectasis and edema of the lungs. The contributing role, if any, played by the succinylcholine apnea cannot be determined or evaluated.

SUMMARY

A case of prolonged apnea following the use of succinylcholine in anesthesia is reported.

The pharmacology of succinylcholine is reviewed briefly. The possible causes of prolonged apnea due to succinylcholine are presented. The etiologic factors in the reported case are suggested and discussed.

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IRREDUCIBLE INTUSSUSCEPTION AND BARIUM PERITONITIS

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Perforation of the colon during or following the administration of a barium enema is probably a more common incident than the reports in the medical literature indicate. Reports of such occurrences mostly concern subacute perforations with local fistulae or abscess cavities rather than contamination of the general peritoneal cavity (1). Barium granulomas have been noted in the appendix, sigmoid colon and rectum (2-5). As might be expected, most of the instances of perforation of the colon have occurred in diseased colons. The diseases most commonly associated with such perforations are diverticulitis, carcinoma, and ulcerative colitis.

With regard to the use of barium enema for the reduction of intussusception in children, we have been able to find but one reference to perforation of the colon during this procedure (6). In the largest series of hydrostatic reduction of intussusception by barium enema (1134 cases), perforation occurred on four occasions. All four patients had symptoms for 48 hours or more and all died after laporotomy. The following case, which survived, is possibly unique in this respect.

CASE REPORT

R. R. (Hospital #70309) a three month old Puerto Rican female infant, was admitted to The Mount Sinai Hospital with a three day history of vomiting and intermittent abdominal pain. The last bowel movement before admission was a soft yellow stool passed two days prior. On the morning of admission, the infant passed a bright red stool and continued to vomit green material. On examination, the child was mildly dehydrated. The abdomen was moderately distended and there was a sense of resistance and mass in the right mid abdomen. During the physical examination the patient passed a bloody stool. A scout x-ray film of the abdomen showed marked dilatation of numerous loops of small bowel containing fluid levels (Fig. 1). No large bowel could be positively identified. The temperature was 100.8°F., the pulse rate was 180 per minute and the respiratory rate was 26 per minute. The white blood count was 9,000 per cu. mm. with 8 per cent segmented polymorphonuclear leukocytes, 10 per cent band forms, 78 per cent lymphocytes and 4 per cent monocytes.

There was a difference of opinion concerning the advisability of performing a barium enema. However, it was done about one and a half hours after admission. A three foot column of barium was used and very mild abdominal massage applied. A free flow of barium was seen to extend to the mid transverse colon where an intussusception was encountered (Figs. 2, 3). Continued pressure of three feet of barium did not reduce or move the intussusceptum after ten minutes and the procedure was discontinued. The infant tolerated the enema well without any observable untoward effect. Surgery was performed through a long right rectus incision about a half hour after the barium enema. On opening the peritoneum, there was an escape of a few cubic centimeters of straw colored fluid and gas with a fecal odor. Numerous

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FIG. 1. Scout x-ray film of the abdomen taken prior to barium enema shows numerous loops of dilated small bowel. No large intestine is outlined.

white clumps and strands of barium were seen throughout the peritoneal cavity. No obvious perforation of the colon was found either at the sigmoid colon or around the intussusception. There was an intussusception of the ileum up to the transverse colon which was not reduceable after fifteen minutes of taxis (Fig. 4). The involved ileum and right colon up to the transverse colon was exteriorized at the upper end of the incision and resected. The protruding loops of ileum and colon were sutured together, Mikulicz fashion, and a catheter was placed into the exteriorized ileum for deflation of the small bowel. A drain was placed down to the left lower abdomen through a stab wound as a safety measure in case of a missed perforation of the rectosigmoid. The specimen revealed an irreducible ileocolic intussusception with severe necrotizing enteritis and hemorrhagic infarction of the terminal ileum (Fig. 4). During the first three post-operative days the course was stormy with intermittent shock, cyanosis, shallow jerky respirations and electrolyte imbalance. The temperature ranged to 103.6°F. and there were focal convulsions of the left face and left upper extremity. Penicillin and chloromycetin were given parenterally from the first day after surgery.

With phenobarbital for the convulsions and appropriate intravenous fluids, there was an improvement in the general status by the fourth day. The ileostomy functioned well from the beginning and the abdomen was soft and deflated. Oral feedings were started and well tolerated. Shortly after this, the ileostomy discharge became semi-soft to firm. The anticipated fluid and electrolyte losses via the ileostomy did not materialize. The volume of discharge ranged from 30 to 170 cubic centimeters with an average of 60 cubic centimeters per day. Except for supplementary clysis on four occasions, the fluid and electrolyte requirements were met by oral intake subsequent to the fourth day after surgery. By the ninth post-operative day the stools became formed and the following day a spur crushing clamp was applied to the ileocolostomy (Fig. 5). Some stool soon appeared per rectum. Thirteen days after the operation, a barium enema showed a free flow from rectum to colostomy without escape of barium from any perforation in the colon. On the twentieth post-operative day when closure of the ileocolostomy was contemplated, the baby developed an enteritis with fever, vomiting and a looser ileostomy discharge. This responded well to dilute feed-



FIG. 2. Barium enema with free flow from the rectum to the mid transverse colon. Notice the cupola effect or cupping in the head of the barium as it meets the intussusceptum which is surrounded by a thin casing of barium.



FIG. 3. Barium enema. X-ray taken a few minutes after the one shown in Fig. 2. Extra-colonic barium is seen alongside the sigmoid colon with its left border curved in conformity with the parietal peritoneum (arrow).



FIG. 4. Specimen of excised irreducible intussusception. The entrapped ileum is infarcted and ulcerated. The tip of the appendix protrudes beyond the intussusception ring.

ings but due to failure to apply the ileostomy bag properly, the skin became irritated around the stoma and there was a further delay in closure of the ileocolostomy. The irritated skin responded best to dry heat by lamp bulb and the application of Neo-Cortef ointment. Thirty-nine days after the ileocectomy, the ileocolostomy was closed. During this procedure, numerous loops of bowel were seen to be adherent to each other and to the abdominal wall incision. There were a few white patches of encapsulated barium encountered in the opera-



FIG. 5. The ileocolostomy, with spur crushing clamp in place, is shown protruding well beyond the skin margin.

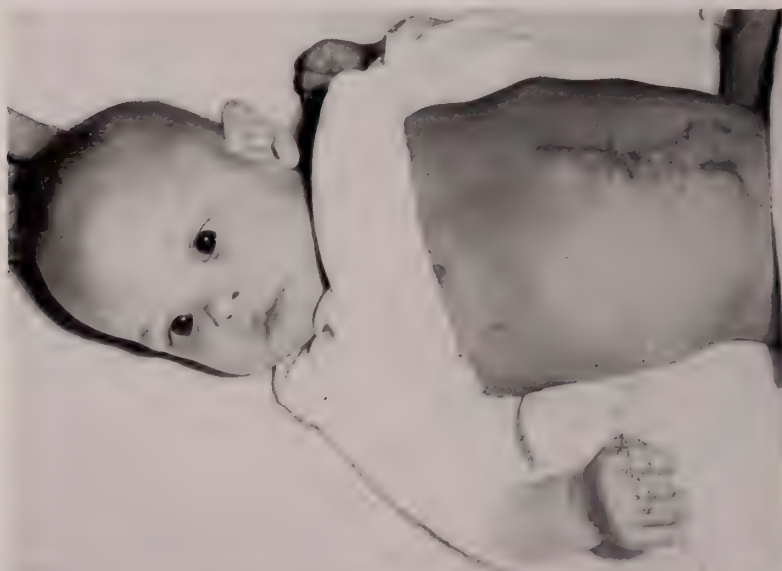


FIG. 6. The baby, 4 weeks after ileocolostomy closure, has a well healed incision and is gaining weight.

tive field around the ileocolostomy. The adherent bowel was left undisturbed. Normal bowel movements started on the day after surgery and feedings were well tolerated. Weight gain was slow but progressive. The baby was discharged approximately two months after admission (Fig. 6). Examination in the clinic three weeks later showed further weight gain and good recovery. A follow-up examination of the child at the age of one year disclosed good weight gain and absence of intestinal disturbances. At this time an x-ray of the abdomen demonstrated numerous flecks of barium scattered throughout the peritoneal cavity (Fig. 8).

DISCUSSION

Barium Enema for Reduction of Intussusception

In Denmark, the barium enema method of treatment of intussusception has gained universal acceptance and is in common use. In a series of 1134 cases, 58 per cent were successfully reduced by this procedure (6). A three or four foot column of barium was usually used with a maximum height of six feet. Columns of barium over four feet were used only in those cases where the duration of symptoms was less than 24 hours. The most important radiologic signs of reduction were (a) complete filling of the cecum and (b) distinct inflow of barium into the ileum. The mortality for those with symptoms less than 24 hours was 3.1 per cent and for those with symptoms more than 24 hours, 26.4 per cent. In four cases treated exclusively with barium enema, four deaths occurred in which autopsy revealed secondary ileo-ileal intussusceptions. It is to be noted that in Denmark, where there is an educational campaign aimed at earlier hospitalization, 80 per cent of the patients are treated within 24 hours of onset of symptoms. Hipsley, in 1926, reported success by hydrostatic pressure in 65 of 100 cases with a 5 per cent mortality (7). However, as Gross (8) has pointed out, quicker hospitalization was obtained in Australia several decades ago than is accomplished in many centers in the United States today. In Clubbe's series published in 1909 (9), the average illness of 17 hours may be compared with Gross' (8) series where the average was 30 hours. These differences of several hours are most important, since the mortality rises precipitously after 24 hours. Today, the mortality in cases with symptoms of 17 hours duration is almost negligible. In this country, 60 to 77 per cent successful reductions of intussusception by barium enema have been reported in smaller series (10, 11). Santulli (10), in a recent appraisal of the barium enema method, advised that palpation of the abdomen be kept at a minimum with no manipulation of an abdominal mass. He is inclined to reserve this method of treatment for those cases with symptoms for less than 24 hours and who show no signs of peritoneal irritation. Ravitch (11), on the other hand, has performed barium enemas on children with intussusception up to five days or more. Gross (8), after an extensive experience with intussusception, believes that it is unwise to adopt the barium enema as a routine therapeutic measure. He believes that surgery is the preferred treatment when there are proper facilities and personnel for performing this. Potts (12) rarely uses an enema for the reduction of intussusception and states that "we still believe that surgery, in general, is the safer procedure".

The disadvantages and dangers of the use of barium enemas for definitive treatment are:

(a) There is a greater risk of recurrence of the intussusception as compared with surgery. The Danish authors with the largest experience in the barium enema routine agree that this has been demonstrated.

(b) There is time lost in a considerable number of patients who subsequently come to surgery. Operation is delayed and is performed on an infant or child who has been subjected to a procedure which is exhausting and which depletes his narrow margin of reserve.

(c) There is the danger of perforation or reduction of gangrenous bowel. The proponents of the barium enema method believe that these complications should not occur with a properly executed enema.

(d) An ileo-ileal portion of an intussusception may be left unreduced.

(e) Associated polyps, tumors or Meckel's diverticulum, which may be responsible for some cases, may be completely overlooked. These can be recognized and corrected if laparotomy is performed.

EXTRAVASATION OF BARIUM

Burt performed experiments on the alimentary tracts of 18 human cadavers whose ages ranged from five and a half months to 82 years (13). Pneumatic pressure was used to determine the force required for perforation. He found that the outer two coats of intestine were the first to perforate and further increase in pressure was required to perforate the mucosa. Intestinal segments of children under twelve years of age were found to support higher pressures before rupturing than corresponding segments of adult intestine. Wangenstein found that the tension on the wall of the intestine increases in proportion to the diameter of the intestine (14). This may account for the rupturing of the larger segments of the alimentary tract e.g. stomach and cecum, at lower intraluminal pressures than segments of smaller diameter, and may also account for the higher pressures required to rupture segments of intestine in children. However, although the sigmoid colon was found to be theoretically almost the strongest segment, it appears to be the most commonly ruptured in clinical experience. The angulation of the sigmoid, and the fact that the rectum is well supported by surrounding structures, except at the rectosigmoid, may explain this; a column of gas or fluid thus injected into the anus is momentarily trapped by the angulation and the force is maximally transmitted to the sigmoid.

Kay and Choy injected sterilized barium into the peritoneal cavity of mice which were killed at monthly intervals up to six months. The barium tended to be lumped into localized masses. Fine adhesions associated with barium granulomas were noted as early as four days after injection. The severity of the reaction was in direct proportion to the quantity injected. Intestinal and bladder distension were also prominent features with larger doses. Adhesions varied from fine bands easily broken, to firm thick strings between viscera rendering separation difficult (15). Kleinwasser and Warshaw injected dogs intraperitoneally with barium sulfate suspensions, mixtures of barium and unsterile stool, and unsterile, sterilized, and filtered stool suspensions (16). The early changes included acute inflammation, free fluid and congestion. All dogs injected with barium alone, survived, and no incidence of significant peritoneal adhesions developed

except in one dog. All dogs injected with barium and stool mixtures died within 48 hours. All dogs injected with unsterile stool died. No reaction occurred in dogs injected with sterile or filtered stool. From animal experiments, it appears that although barium alone may produce some adhesions, the important factor which determines the formation of dense adhesions, obstruction and morbidity, is the concomitant introduction of infective material into the peritoneal cavity. In the case presented above, numerous loops of bowel were found to be adherent to each other and to the abdominal wall. Time will tell whether the contraction of adhesions will lead to intestinal obstruction. There has been no significant long term follow-up of patients who have survived perforation of the colon with extravasation of barium. A good review of the literature is given by Hamit (17).

The diagnosis of perforation of the colon during barium enema is ideally made shortly after it occurs. The barium frequently collects in the space between the descending or sigmoid colon and the lateral abdominal wall (1). It is visualized lateral to the barium filled colon with the free barium showing a smooth left border where it is delimited by the parietal peritoneum (Fig. 3). Pneumoperitoneum, pneumomediastinum and subcutaneous emphysema may be present and detected either clinically or by x-ray. Clinical signs include various degrees of shock, distended tympanitic abdomen, subnormal temperature which rises as peritonitis progresses, and positive Hamman's sign or mediastinal crunch. At operation, malodorous gas or fluid may escape upon incising the peritoneum; emphysema of the omentum or retroperitoneal tissues may be present. If the perforation is very small and not readily detected, an area of subserosal hemorrhage in the area of the perforation may give a clue to its location. The escaped barium is generally distributed as white strings or clumps.

Perforation of the bowel with escape of barium requires immediate laparotomy with closure of the perforation and proximal decompression. The larger obvious masses of barium clumps may be removed, but too much time with manipulation of bowel should not be taken in order to try to rid the peritoneal cavity of all barium. This material is walled off in a manner which is usually innocuous. We know of a few children whose x-rays have shown flecks of barium in the abdominal cavity for many years. The area of closure is drained to allow a tract of egress should the closure leak. A tube cecostomy will suffice for proximal decompression in cases of simple perforation of the sigmoid without other concomitant pathology. Where there is associated pathology, e.g. irreducible intussusception, atresia of the ileum, volvulus, one must obtain decompression and correct the pathology in the simplest and least traumatic manner. We have had experience with two such cases. In the first instance, a newborn infant, there was an atresia of the ileum. The upper rectum at the peritoneal reflection anteriorly was hemorrhagic, but no obvious perforation was seen. A drain was placed down to this area through a left lower quadrant stab wound. The atresia was resected and an ileostomy performed. This functioned well with discharge of semi-soft stool. After five weeks the ileostomy was anastomosed to the cecum. In the second case, reported above, the irreducible intussusception was exteriorized and resected, leaving an ileocolostomy which discharged a semi-formed to formed stool. In another instance where an ileostomy was performed for meco-



FIG. 7. The transparent ileostomy bag protects the skin and allows visualization of the character and amount of ileostomy discharge.



FIG. 8. X-ray of the abdomen taken nine months after extravasation of barium into the peritoneal cavity. There are numerous patches of encapsulated barium best demonstrated along the left colon.

nium ileus, the ileostomy functioned satisfactorily for many weeks (18). We mention these experiences to point out that, although babies do not tolerate well the loss of succus entericus, a better understanding of electrolyte needs has enabled us to safely prolong the time of closure of the ileostomy should this be necessary. In cases of perforation of the colon, where an ileostomy becomes necessary, closure of the ileostomy is delayed for at least two weeks to make certain that the perforated colon is healed. We have found that a transparent ileostomy bag cemented to the skin serves the double purpose of protecting the skin and collecting the ileostomy discharge for measurement and electrolyte analysis (Fig. 7).

SUMMARY

A case of perforation of the colon with escape of barium and irreducible intussusception, with surgery and survival is presented. The pathology, diagnosis, and treatment of extravasation of barium subsequent to perforations of the colon is reviewed. A brief discussion of ileostomies in infants is added.

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CLINICAL CONFERENCE ON MEDICAL HAZARDS OF PREGNANCY

The Mount Sinai Hospital

Monday, December 17, 1956

1. Introductory Comments.....Dr. Alan F. Guttmacher
2. Toxemia of Pregnancy
 Case Report.....Dr. Nathan G. Kosovsky
 Discussion.....Dr. Marvin F. Levitt
3. Afibrinogenemia
 Case Report.....Dr. William J. Shapiro
 Discussion.....Dr. Martin C. Rosenthal
4. Rheumatic Heart Disease
 Case Reports.....Dr. Ira J. Gelb
 Discussion.....Dr. Simon Dack

Chairman King:

About four years ago, there was added to this hospital, the Department of Obstetrics. Since that time, the medical and allied services have had the opportunity of observing and studying both the hazards and complications of pregnancy and parturition. This evening's program is devoted only to "The Medical Hazards of Pregnancy"; problems of which we had been aware, but which we now know from closer experience.

Not all of the medical hazards can be included in this program, because of the exigencies of time, and so we have chosen three of the most important and challenging medical problems which confront the obstetrician and his medical colleagues. These are the common hazards of toxemia and rheumatic heart disease, and the less common, but intriguing and serious entity of afibrinogenemia. To discuss these, we will call on members of the medical department, who are interested respectively in renal disorders, hematology and cardiology.

Before doing this, we have asked Dr. Alan Guttmacher, who is Director of the Department of Obstetrics and Gynecology, to open the discussion with introductory remarks regarding the overall problem as he knows it.

INTRODUCTION

Dr. Guttmacher:

I have determined to talk briefly, and to discuss only two topics. First, I would like to tell you how the Department of Obstetrics is organized in regard to the interplay of medicine and surgery, with obstetrics. As Dr. King said, our department is very new. As a matter of fact, I tease by saying that The Mount Sinai Hospital is the oldest primipara in medical history, she was a hundred years old when her first child was born, beating Sarah by a scant ten years; Sarah was ninety.

This new department had the opportunity to organize itself according to any plan selected. Most obstetricians feel that they are experts in all fields of medicine. They imagine themselves pseudo-experts in cardiology, diabetes, hematology,

ogy, hypertension in pregnancy or what you will. It seemed better to us to admit we were not expert in these various fields, and to organize special clinics presided over not by obstetricians, but by internists, who make these particular modalities their life's work. With the tremendous cooperation given by The Mount Sinai Hospital staff we were able to establish among our special clinics, five clinics devoted to the medical problems of obstetrics. You shall hear from three tonight. The diabetes and pregnancy clinic over which Dr. Dolger presides so ably, and the pregnancy chest clinic which Drs. Selikoff and Dorfman conduct so brilliantly will not report tonight.

I feel that our innovation in antenatal care has been hugely successful. First, it makes possible much better care for the patients, with every modern facet of diagnosis and therapy available. In the second place, it creates excellent teaching units. Our House Staff profits greatly from this, The Mount Sinai Hospital prenatal plan. In the third place, it presents a good method for collecting similar problem cases of pregnancy, so that studies and publications may result therefrom.

The second topic which I want to discuss is the handling of therapeutic abortion at The Mount Sinai Hospital. As you know, there are many ways of validating therapeutic abortion in various hospitals. One simple technique is to have the head of Obstetrics pass upon or reject each case, or simply to allow two senior men of the staff to state on the chart the necessity for this procedure; or thirdly to establish an abortion committee.

I think the first method is open to many objections, not least of which is that it places a great burden on one man, and endows him with a kind of omniscience which most of us do not possess.

The second technique, which simply allows two senior staff men to certify the necessity for interruption of pregnancy, creates leniency in regard to therapeutic abortion, which has several drawbacks. Very often the men who write the notes have not had the opportunity to see, care for, and follow patients with this particular ailment through a safe pregnancy. Perhaps such cases have been delivered on the obstetric service with safe results. Then too, very often consultants are importuned by families or other physicians, to certify an abortion to which they are luke-warm, compelling them to assume a certain enthusiasm for pregnancy termination which they do not actually possess. Staff certification makes for a much higher abortion rate. To some of you, such a high rate may be preferable. Those of us in charge of a service with statistics published, analyzed and discussed develop a self-conscious attitude toward a high incidence of therapeutic abortion. That is, if it is considerably higher than other teaching institutions of the same variety.

For these many reasons, we elected not to have staff members validate therapeutic abortions, but to put the decision up to a committee. As many of you know, the committee is composed of the Chief of Obstetrics, the Chief of Psychiatry, a senior member of the Departments of Medicine, Surgery and Pediatrics. The committee meets each week. Forty-eight hours before the meeting letters from two consultants must be filed with the committee stating the ne-

cessity for the therapeutic interruption. These letters are circulated among the members of the committee before the meeting. One of the consultants and the obstetrician who proposes to carry out the procedure, must be present at the meeting to answer additional questions when necessary.

This scheme perhaps may be cumbersome, but we feel it is effective. Table I reveals that we have had only 117 requests for therapeutic abortion during the four year existence of the Abortion Committee. During this period, The Mount Sinai Hospital has had almost 16,000 deliveries. You may notice that the committee validated 84 per cent of the requests. Incidentally, the vote of the committee must be unanimous. In almost every instance, the physician within whose particular field the indication rests, has the leading vote, and we are very likely to follow his decision in the matter. The fact that we have had relatively few cases presented doesn't mean that these are the only cases which have originated within the hospital. Many cases are not brought before the committee, because one of its members has been informally consulted. Perhaps the physician calls me and says, "What has the committee done about multiple sclerosis?" or, "What is the committee's attitude toward Hodgkins Disease?" or, "What action has the committee taken about this and that?" I tell the inquirer what the experience has been if we have had such a case. Despite earlier adverse action of the committee, any staff doctor is still privileged to bring the case up for consideration; but if he thinks he is going to be turned down, it is likely he will not. As a result we validate more than eight cases out of ten which are considered; most of the cases which would be rejected never come before the committee as a whole.

Table I demonstrates that the chief indication for which therapeutic interruption of pregnancy is requested at The Mount Sinai Hospital is psychiatric. As you see, of the 117 requests which have been made 45 or 39.3 per cent have been on psychiatric grounds. You will see that we rejected 8 of the 45 psychiatric patients brought before us. In other words, psychiatric indications represent four in ten and have become, by all odds, the most common condition. The most frequent indication is no longer a damaged heart, kidney or lung; such organic conditions, you will notice, are far down on the list.

The second commonest indication, 27 per cent, is eugenic, more correctly cacogenic, and as you see, rubella represents, by all odds, the commonest of these problems. We continue to do interruptions of pregnancy for rubella if the woman is less than 12 weeks pregnant when she has the rash. That is, only if a member of the Infectious Disease Division of the Health Department, or a pediatrician of qualified standing, attests to the fact in writing that the case is truly rubella.

What about the cases of rubella we did not interrupt? One was, I believe, 13 weeks pregnant; in the other two, the committee felt that the certainty of rubella was open to question. The Mount Sinai Hospital is the only institution in New York which still does therapeutic interruptions for rubella. But since the most recent publication claims that 17 per cent of such children are abnormal, the committee feels rubella presents an urgent indication.

TABLE I

Summary of therapeutic abortions, November 1, 1952–November 1, 1956

	Number	Aborted	Re- jected	Steri- lized
1. Psychiatric 46—(39.3%) Per cent aborted, 80%				
Psychotic with suicidal intent.....	45	37	8	13
Feebleminded.....	1	0	1	
2. Eugenic 32—(27.4%) Per cent aborted, 87%				
Rubella.....	28	25	3	0
Hemophiliac Carrier.....	2	2	0	2
Child with muscular dystrophy.....	1	0	1	0
Post-conceptual radio-therapy.....	1	1	0	0
3. Malignancy 14—(11.9%) Per cent aborted, 93%				
Breast.....	6	6	0	2
Cervix.....	2	2	0	0
Thyroid.....	2	2	0	1
Melanoma.....	2	2	0	0
Hodgkins.....	2	1	1	0
4. Cardio-vascular 8—(6.8%) Per cent aborted, 100%				
Cardiac.....	6	6	0	6
Varicose Veins.....	1	1	0	0
Advanced arteriosclerosis—diabetic.....	1	1	0	1
5. Renal 4—(3.4%), Per cent aborted, 100%				
Renal failure.....	2	2	0	1
Urinary tract infection, solitary kidney.....	2	2	0	2
6. Neurological 3—(2.5%) Per cent aborted, 0%				
Multiple Sclerosis.....	2	0	2	
Progressive Neurologic disorder.....	1	0	1	
7. Gastro-intestinal 3—(2.5%) Per cent aborted, 67%				
Pernicious vomiting.....	1	0	1	0
Ileojejunitis.....	1	1	0	0
Ulcerative colitis.....	1	1	0	0
8. Ocular 3—(2.5%) Per cent aborted, 67%				
Detached retina.....	1	0	1	
Retinal Thrombosis prev. preg.....	1	1	0	1
Congenital cataracts—vision in one eye.....	1	1	0	
9. Pulmonary 2—(1.7%) Per cent aborted, 100%				
Tuberculosis, lobectomy, little functioning tissue.....	2	2	0	2
10. Orthopedic 2—(1.7%) Per cent aborted, 100%				
Chronic back with radicular involvement.....	1	1	0	1
Congenital absence of both legs—partially ambulatory.....	1	1	0	1
Total.....	117	98	19	33
		84%	16%	34%

Table I shows that there were two cases in which the mother had had hemophiliac sons.

Malignancy has risen into a prominent position, about 12 per cent. There were two cases of Hodgkins disease, one of which was refused by the committee. In the other the patient was eight weeks pregnant when Hodgkins disease was diagnosed. This was a very progressive type of Hodgkins disease and the radio-

TABLE II
Proportion of therapeutic abortions performed to deliveries

Total Deliveries	15,642	Total Therapeutic Abortions	98	Proportion 1:160
Private Patients Delivered	10,472	Total Therapeutic Abortions	68	Proportion 1:154
Clinic Patients Delivered	5,170	Total Therapeutic Abortions	30	Proportion 1:173

therapists were anxious to administer radioactive substances and x-ray immediately. Therefore the pregnancy was interrupted; it was not felt that pregnancy itself worsens Hodgkins Disease.

The cardiovascular group is in fourth place, constituting less than 7 per cent of all cases requested. I dare say if the same list had been presented to you ten years ago, cardiac disease and pulmonary tuberculosis would probably be the two most common indications for interruption of pregnancy. But with the great developments in the care of the cardiac and the tuberculous woman, it is almost never necessary to interrupt pregnancy in patients with these complications.

The six cardiac cases which were interrupted included two patients who had had coronary thrombosis and were having frequent angina. The other four patients interrupted for cardiac disease had had, or were in failure.

The renal group is composed of two cases in renal failure and two patients with solitary kidneys and chronic urinary tract infection. None of the neurological group rated interruption of pregnancy. In the gastrointestinal group there was one case of ulcerative colitis, and one of ileo-jejunitis, among scores of pregnant women at our institution with similar pathological processes.

There were three ophthalmological cases, and there were but two cases of pulmonary disease. These were both complicated. One patient had tuberculosis, diabetes, and bronchiectasis; the other had chronic tuberculosis, severe asthma and reduced pulmonary ventilation from a lobectomy.

Table II shows the proportion of therapeutic abortions to the total number of deliveries. The rate was one therapeutic abortion to 160 deliveries. If we eliminate the cases done for rubella, the rate declines to one to 222. The Mount Sinai Hospital's rate is a relatively high one for the country at large. The Margaret Hague Hospital boasts that they have done one therapeutic abortion to every 12,500 cases. The Johns Hopkins Hospital does about one therapeutic abortion to every 400 cases. All over the country the large university clinics, and the large teaching clinics, have a relatively low rate, that is the proportion of therapeutic abortions to term deliveries is relatively small. In the non-teaching hospitals, there is ordinarily a higher rate than in institutions like our own.

Table II also breaks down the incidence into private and ward patients. You will note the incidence is approximately the same.

The marital status of the patients is interesting. Table III shows that a very high proportion of the psychiatric cases were single. Forty-three and a half per cent of the psychiatric cases were single, and in the non-psychiatric, only 4.2 per cent were single. This has many social implications. Among them, perhaps the unmarried psychotic is particularly vulnerable to impregnation.

Table IV shows that we are becoming more conservative in regard to psy-

TABLE III
Marital status

Married	94	80%
Single or Divorced	23	20%
	117	
Percentage married-psychiatric indication		56.5%
Percentage married-nonpsychiatric indication		95.8%

TABLE IV
Proportion of psychiatric requests in two periods

First forty cases reviewed by Committee—50% of total
Second forty cases reviewed by Committee—27.5% of total

chiatric indications. In the first 40 cases reviewed by the committee, psychiatric indications were 50 per cent of the total cases presented. In the second 40 cases reviewed by the committee, they formed only 27½ per cent of the total.

In these few minutes I have demonstrated that therapeutic abortion for organic disease at The Mount Sinai Hospital, is a relatively infrequent necessity due to the fantastic developments in internal medicine. It is very rarely incumbent upon the obstetrician to interrupt pregnancy because of heart, lung or kidney disease; these at one time formed the important triad of indications for therapeutic termination of gravidity.

Chairman King:

One of the common and serious hazards of pregnancy is the toxemia of pregnancy. Before discussing this, we will have a case presented by Dr. Nathan G. Kosovsky.

TOXEMIA OF PREGNANCY
Case Report

Dr. Nathan G. Kosovsky:

This is the first admission to The Mount Sinai Hospital of a 32 year old white female, gravida two, para one, who entered with the chief complaint of headache and nausea of two days duration. The general medical history was essentially negative, save for a long term tendency toward obesity. Obstetrically, four years prior to admission, the patient had an uneventful normal spontaneous delivery of a healthy, mature infant at another hospital. During that pregnancy, no evidence of hypertension or excessive weight gain was noted. Since that time, no blood pressures had been taken.

When first presenting for medical care during the present pregnancy, the patient was noted to be 20 weeks gravid. The last menstrual period was January 3, 1955, the expected date of confinement, November 6, 1955. Weight was 160

pounds, blood pressure 120/80, and the general medical and obstetrical examinations were negative. Funduscopy examination was unremarkable.

During the next six weeks, the patient gained 12 pounds despite oral and intramuscular diuretics. From that time until the 32nd week of her pregnancy she did not come to the clinic nor could she be located. When she returned to the clinic her blood pressure was 160/90, and examination of her urine revealed 4 plus albumin. There was moderate ankle edema at this time. The weight was 185 pounds. The fundi were negative. No polyhydramnios was noted.

A strict low sodium diet, complete bed rest and moderate sedation with phenobarbital was immediately instituted. The patient was seen frequently during the next three weeks, and despite a nine pound weight loss, the blood pressure remained about 160/90, and the urine continued to show 4 plus albuminuria.

At 35 weeks of pregnancy, the patient suddenly developed headache, nausea, insomnia, and complained of blurred vision. She was hospitalized immediately. On examination, the blood pressure was 240/180, the pulse was 92 and she was afebrile. She was noted to be drowsy and complained of severe coronal headaches. Funduscopy examination at this time revealed generalized arteriospasm without hemorrhage or exudate. The heart and lungs were negative. Abdominally, the fundus was measured to be three finger breadths above the umbilicus. The fetal heart was regular at 132 per minutes. The abdomen was soft. There was no labor present. The extremities showed 2 plus pitting edema extending to the knees bilaterally and the reflexes were generally hyperactive. No clonus or Babinski were noted.

The pelvic examination at this time revealed a long, soft cervix which was 2 centimeters dilated. The membranes were intact, and the vertex was presenting at minus two station. There was no vaginal bleeding noted. The fetus was small and was estimated at 2400 grams.

The patient was treated with a regimen of intravenous fluids; morphine, 15 milligrams of morphine every four hours; magnesium sulphate, ten grams immediately, and five grams every six hours; phenobarbital, 120 milligrams every six hours; and penicillin and streptomycin. Despite therapy, the blood pressure continued at 200/150 during the next three hours. The output of urine during this period was scant, dark and persistently showed 4 plus albumin. Five cubic centimeters of Veralba® was added to the infusion, which was then adjusted to stabilize the blood pressure at 180/110.

Five hours following admission, the membranes were ruptured revealing meconium stained amniotic fluid. However, the fetal heart tones remained good. Pelvic examination at this time was unchanged from that on admission. After a five hour latent period, ten hours after admission, during which time, despite the Veralba® drip, the blood pressure rose to 240/170, labor spontaneously began. After a two hour and ten minute labor, with a seven minute second stage, the patient was delivered, without complications, of an 1840 gram drowsy female infant which required two tenths of a milligram of Nalline® and five minutes of Emerson resuscitation before spontaneous respirations were established. The child did well thereafter.

During labor, the blood pressure at no time exceeded 190/140. Examination of the placenta at the time of delivery revealed several small infarcts on the maternal surface, in addition to one small fresh hematoma. There was no unusual hemorrhage noted during the delivery.

Immediately post partum the patient was given morphine and phenobarbital and the blood pressure remained fairly stable at 180/130, the pulse was 92 per minute and the temperature was normal. During the first twelve hours of hospitalization, while the patient received 450 cc of fluid intravenously, the output was 365 cc of 4 plus albuminuric, very dark, concentrated urine. The patient was placed in a dark room, and medication was continued as before, and during the first post partum day the patient's condition was unchanged. The blood pressure ranged between 180/130 to 200/150. The urine totalled 370 cc for the next 24 hours, despite approximately 2,000 cc of intravenous fluids. The urine again showed 4 plus albuminuria.

During this day, the patient was drowsy and disoriented, but no nausea or headache was noted. By the second post partum day, however, diuresis began, with approximately 2,000 cc of urine. This showed 2 plus albuminuria. The blood pressure, however, remained in the 190/120 range.

Over the next six days the patient improved. Diuresis continued with gradually decreasing albuminuria to zero, and slow resolution and stabilization of the hypertension at 160/90.

Throughout her hospitalization, laboratory examinations including blood urea nitrogen, uric acid and creatinine, expressions of her renal function, were all normal. The patient was discharged feeling very well, with a blood pressure of 160/90. She was seen six weeks post partum, when the blood pressure was 170/100, the weight was 161 $\frac{3}{4}$ pounds, and the urine was negative.

Chairman King:

One of the members of our medical service who is interested in the study of renal diseases, Dr. Levitt, became interested in toxemia and has served as the medical consultant to the toxemia clinic. We will ask him to discuss the question of "Toxemia of Pregnancy."

Discussion

Dr. Marvin F. Levitt:

This patient has been followed for some time and has had a persistence of the high blood pressure since her delivery. There was some element of essential hypertension prior to the pregnancy, and the likelihood is that she is a patient with essential hypertension who developed a superimposed preeclampsia during labor and shortly thereafter.

When we became interested in the subject of preeclampsia, it became apparent to us that there was a marked dearth of data regarding the train of renal hemodynamic events which transpire in a normal pregnancy. Although there was a tremendous amount of information regarding renal function in preeclamptic and eclamptic patients, there was very little of this type of data in patients who had

undergone a perfectly normal pregnancy without any evidence of previous or existing hypertension.

In Figure 1 the renal plasma flow is plotted against the week of pregnancy in 17 normal pregnant females. It is apparent that the mid-trimester of normal pregnancy is characterized by a very marked renal hyperemia. The dotted area represents the normal renal plasma flow of comparably sized women, and the crosses represent the marked increments which are apparent in the mid-trimester of normal pregnancy. Note that as a normal pregnant woman enters the third trimester, there is a considerable fall in renal plasma flow toward normal levels.

Figure 2 shows the results of the simultaneous measurements of filtration rates in the same pregnant patients. There is a markedly supernormal filtration rate,

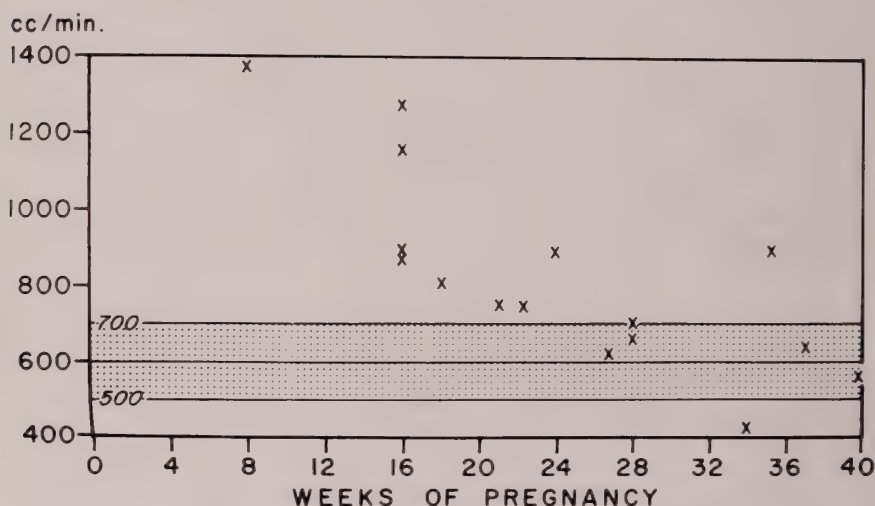


FIG. 1. Renal plasma flow throughout normal pregnancy.

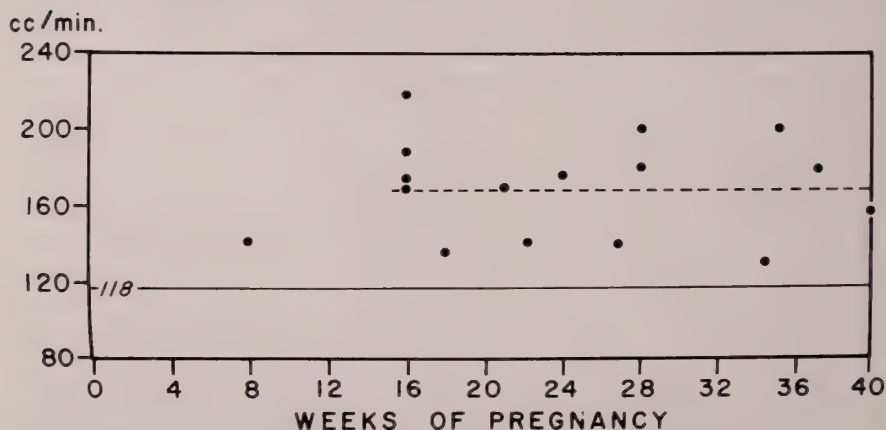


FIG. 2. Glomerular filtration rate throughout normal pregnancy.

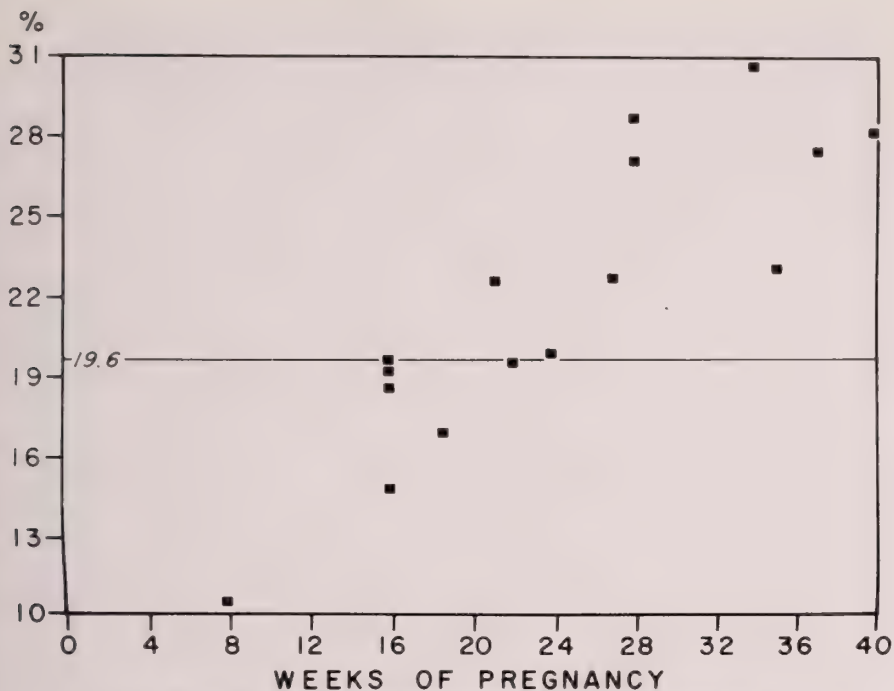


FIG. 3. Changes in filtration fraction during normal pregnancy.

approximately 50 per cent beyond normal, which is present in the middle trimester and persists in the last trimester. The filtration rate remains elevated in the last trimester of pregnancy in contrast to the renal plasma flow which falls toward normal.

In Figure 3, the filtration fraction is plotted against length of pregnancy. As expected from the changes in renal plasma flow and filtration rate, the filtration fraction tends to be low early in pregnancy, rises toward normal in the mid-trimester, and then supersedes normal, approaching 50 per cent above normal in the third trimester of normal pregnancy.

Figure 4 summarizes the changes in normal uncomplicated pregnancy. The renal plasma flow becomes markedly supernormal in the mid-trimester, falls toward normal as the pregnancy enters the third trimester. Filtration rates remain definitely supernormal throughout pregnancy, and consequently the filtration fraction rises during pregnancy.

I have gone over this data very quickly, but I'd like to spend a little more time discussing the implications of these changes in renal circulation and renal hemodynamics which characterize the normal pregnant woman.

The vasodilatation noted in the kidney during the mid-trimester apparently is taking place throughout the body of the normal pregnant woman. Consequently, there is a fall in mean peripheral resistance throughout normal pregnancy with an attendant fall in blood pressure (Fig. 5). Such a fall in blood pressure can easily obscure the presence of an antecedent hypertension, and ap-

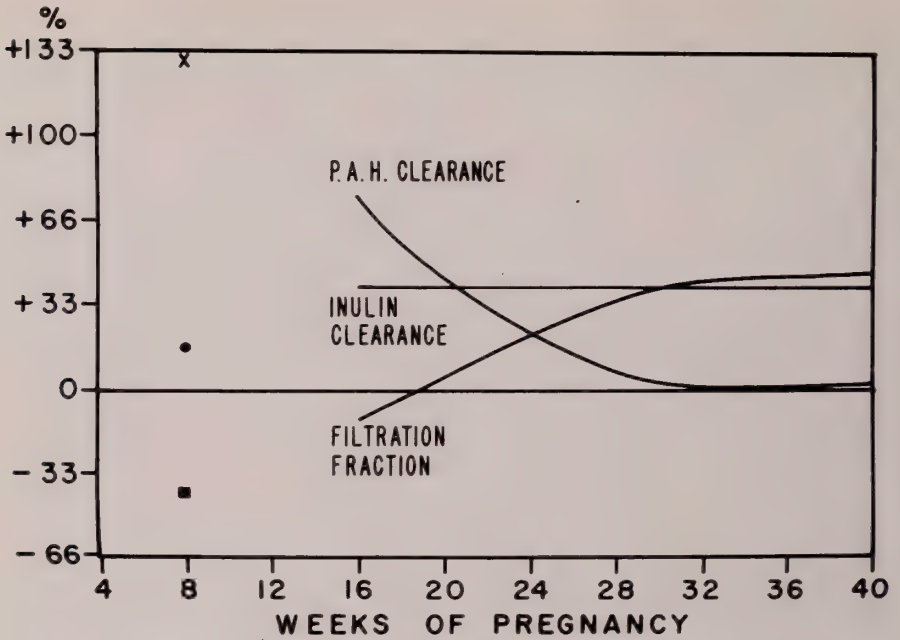


FIG. 4. Summary of changes in renal hemodynamics during normal pregnancy.



FIG. 5. The mid-trimester fall in blood pressure.

parently such is the situation in the patient that was presented tonight. In the last trimester, the normal pregnant woman undergoes a generalized vasoconstriction. It is not hard to imagine that the patient with antecedent hypertension may be particularly vulnerable to the normal vasoconstriction of the third trimester. A rise in blood pressure in the third trimester may not necessarily be attributed to preeclampsia, but may instead be the return toward hypertensive levels which had been obscured by the vasodilatation of the mid-trimester.

In terms of this data in the normal pregnant woman the changes which take

place in preeclampsia become particularly conspicuous. There are a host of measurements available to indicate that the preeclamptic woman undergoes a slight fall in renal plasma flow, and a marked fall in filtration rate. When these changes are compared to renal hemodynamics in the normal woman, they are not as impressive as when they are compared to those obtained in the normal pregnant woman. It appears that the development of preeclampsia may represent an exaggeration of the ischemia which takes place in the third trimester of normal pregnancy. If this is so, it seems reasonable that the hypertensive patient, or the patient with a tendency toward hypertensive disease, would be particularly prone to the development of this superimposed ischemia. The fact that hypertensives are so likely to develop a superimposed preeclampsia would be in accord with this hypothesis.

It is possible that the subject who has a latent hypertension, or a tendency to the development of hypertension, is particularly vulnerable to the generalized vasoconstriction which takes place in the third trimester. It is not impossible, in this point of view, for a patient with latent hypertension, without any previous evidence of the hypertensive process, to develop a preeclampsia as the first manifestation of the hypertensive diathesis. Actually, as more workers have studied the long term course of preeclamptics, it has become increasingly apparent that the overwhelming majority of preeclamptics ultimately become patients with essential hypertension. According to this point of view, the ill effects of a superimposed preeclampsia will depend not so much upon the length or the severity of the preeclampsia, but rather upon the underlying state of the blood vessels when the preeclampsia develops.

A fall in blood pressure from preeclamptic levels to normal levels following pregnancy does not, therefore, rule out the presence of underlying essential hypertension. In our clinic we try to evaluate the nature of the third trimester hypertension by referring to the first trimester readings (when available). Of all patients with third trimester hypertension, on whom first trimester readings are available, 80 per cent show evidence of blood pressure elevation in the first trimester. This finding is often obscured by the vasodilatation of the second trimester.

These findings suggest that preeclampsia may be a manifestation of antecedent hypertension or of a hypertensive diathesis which renders the patient particularly susceptible to the vasoconstrictive influences of the third trimester. The preeclamptic process is simply an exaggeration of the normal ischemia which takes place in the third trimester.

The kidney is not the only organ to be rendered ischemic during the preeclamptic process and there are a considerable number of measurements which indicate that the uterus and placenta likewise become extremely ischemic. In fact, the problem of the ischemic and infarcted placenta often poses the biggest problem in the therapeutic management of these patients.

I would like briefly to mention the wonderful results that have been generally obtained in the management of the preeclamptic. The frequent observation of the pregnant woman, the availability of hospital beds, the salt free diets, and

the available diuretics have cut down the frequency of the treacherous eclampsia to a very considerable extent. We have not lost a single woman from eclampsia in the two-and-a-half years we have been interested in these preeclampsies. But this is not an experience typical of The Mount Sinai Hospital; it has become a general experience. If these women are watched very carefully and the r weight controlled, and if they are hospitalized with the first sign of persistent hypertension or albuminuria, the results are generally excellent. The effect of salt free diets, the variety of diuretics we have available, have all tended to cause remarkable elimination of the eclamptic syndrome itself.

Of course there is an occasional group of patients in whom sedation and bed rest and the usual conservative measures are not to any avail, and in this group there has been an enthusiastic attempt to use the anti-hypertensive agents. Our experience with the anti-hypertensive agents has been somewhat limited. But we must admit that certainly the more benign and the milder of the anti-hypertensive agents are perfectly safe and we have not seen eclampsia in any patient who has been treated with the anti-hypertensive agents. However, we believe the progress is not so much in the use of the anti-hypertensive drugs as it is in the careful dietary and diuretic management of the preeclamptic subject.

Where we are not quite so proud of our record is in the frequency of foetal death as a sequella of uterine ischemia. The decision as to when to empty the uterus is often a very difficult one. When the child is of good size, as it was in the patient presented here tonight, and the pregnancy is of 37 to 38 weeks duration, it is possible to evacuate the uterus if annoying manifestations of preeclampsia persist. Here a living child usually results. It is in the pregnant woman who has a persistent hypertension, or albuminuria, or both, in whom the fetus is quite small and the pregnancy in the early thirties, that a very difficult decision must be made. We have all had the experience of observing such a patient after deciding to wait for several more days or several more weeks to be told the following morning that the fetal heart had stopped, or that an abruptio placentae had occurred, or that there had been uterine bleeding. There is no pat formula for the decision as to when the uterus must be emptied, and one must consider very carefully the previous hypertensive history, the persistent manifestation of preeclampsia, the size of the baby, and the rate at which the baby is growing. I must admit that at the beginning I felt very inadequate next to the obstetrician who carefully palpates the abdomen and tells me the baby is 2,000 grams, 2400 grams, 2700 grams, until I realized that their accuracy was no better than my accuracy of measuring filtration rates, which is about 50 per cent, so I have gotten to be as cocky as they are; and we try to help estimate the size of the baby.

With all these considerations the decision is often extremely difficult. In that interim of pregnancy in which the child is barely viable, often two to three weeks of continuing the pregnancy affords a greater chance of foetal survival. Such delay is sometimes responsible for sudden problems precipitated by placental ischemia. However, if it is appreciated that the permanent vascular effects of preeclampsia do not depend upon the length and severity of preeclampsia but

rather upon the vascular state prior to pregnancy, it makes it easier to wait for foetal viability.

The effect of the anti-hypertensive drugs on the placental blood flow is unknown. There is no evidence that these agents actually increase the blood flow through such an ischemic and infarcted placenta.

I would like to make one other point that has become apparent to us as we have studied these preeclamptic patients. It is not uncommon for preeclampsia and even eclampsia to develop in labor and in the first day or two post partum. In fact, most of our eclamptics have been patients who have convulsed shortly after labor, or in the first day post partum. In part this may be due to the fact that such patients have generally not been followed as carefully as those who are watched throughout pregnancy and before labor. Not infrequently we are called to the Obstetrical Service to see a patient who has become markedly hypertensive, and developed severe albuminuria shortly after labor or in the first day post partum. This disease is preeclampsia and can result in eclampsia during the first 24 to 48 hours after the delivery. If blood pressures were taken throughout labor, and possibly in the first day thereafter, many of these serious complications in the post-partum preeclamptics could be avoided. Certainly the use of any vasoconstrictive drug in a subject who is particularly vulnerable to the ill effects of any further physiological vasoconstriction to the kidney, placenta and probably the brain and heart, should be strictly avoided.

In essence, I would like to emphasize that it has become our belief that preeclampsia represents one manifestation of the course of hypertensive disease; that in most of our patients it is superimposed upon antecedent essential hypertension. We believe that even when there is no history of antecedent essential hypertension, preeclampsia may be the first concrete manifestation of an underlying hypertensive diathesis which exaggerates the evil effect of the vasoconstriction of the normal third trimester.

Acknowledgment

The data presented in this discussion was collected in conjunction with Dr. Ezra Zohar.

Chairman King:

One of the rarer, rather dramatic, and serious hazards of pregnancy is the entity of afibrinogenemia. We will have such an instance presented by Dr. William J. Shapiro.

AFIBRINOGENEMIA

Case Report

Dr. William J. Shapiro:

The patient is a 31 year old Puerto Rican female, gravida seven, para six. The expected date of confinement was September 12, 1956.

Her past obstetrical history revealed that she had four pregnancies in Puerto

Rico, all of which terminated at or near term by spontaneous delivery of normal infants. Her last pregnancy was concluded here in New York, at St. Clare's Hospital. It was a normal, uncomplicated pregnancy and delivery, except for a positive serological test for syphilis for which she was treated adequately with nine million units of penicillin.

She was seen for the first time during this pregnancy when she was 23 weeks gravid. The initial examination revealed that she had a blood pressure of 120/80. The heart and lungs were unremarkable, and funduscopic examination was negative. The size of the uterus was consistent with the dates of amenorrhea, namely 23 weeks.

Because of a history suggestive of convulsive disorder an electroencephalogram, neurologic examination and skull films were done, and all revealed no significant abnormalities. All laboratory findings were normal, except for a slightly positive Mazzini test. In view of the previous adequate treatment, retreatment was not indicated.

The patient was seen in the "Prenatal Clinic" from the 24th to the 30th week of gestation on three separate occasions. At all times there were no signs of toxemia, and the pregnancy was thought to be progressing normally. On July 2, 1956, at 30 weeks gestation, she was admitted to the labor floor with a history of the onset of sudden severe abdominal pain followed by bright red vaginal bleeding of seven hours' duration. Fetal movements were felt by the patient prior to the onset of the pain.

On admission to the labor floor, the patient appeared to be acutely ill, complaining of severe, persistent abdominal pains. The blood pressure was 150/90. The pulse was 120. The heart and lungs were unremarkable. On abdominal examination the abdomen was found to be tense with board-like rigidity. The uterus was extremely tender and palpated to the size of a 40 week gestation. The fetal heart tones were not heard. On vaginal examination, the cervix was found to be 2 cms. long, firm, and 2 cms. dilated. The presenting fetal part could not be palpated. Examination of urine revealed that she had a 4+ albuminuria. The hemoglobin was 9 gms per cent. Two weeks previously, in the clinic, the hemoglobin was 12 gms per cent. Blood samples were drawn, coagulation studies were started, and a unit of whole blood was administered.

The patient was taken to the delivery room. Under sterile precautions, the patient was found to be 2 cms. dilated, the presenting part was determined to be a vertex, no placental tissue could be palpated. The amniotic sac was artificially ruptured. The patient received 1000 cc of whole blood during this procedure and there was no evidence of shock. A desultory labor began and continued for four hours. A dilute solution of Pitocin®, 8 minims per 1000 cc of 5 per cent dextrose in water was started.

Table V lists the results of the coagulation studies on blood which was drawn eight hours after admission to the hospital.

It was felt that we were dealing with the syndrome of hypofibrinogenemia, and accordingly, the patient received three grams of fibrinogen. At this time, pelvic examination revealed the cervix to be 5 cms. dilated. The presenting part

TABLE V
Coagulation studies prefibrinogen

Clotting Time.....	21½ min. (15)
Prothrombin Time.....	23.4 sec. (12)
10% Prothrombin time.....	25.4 sec. (25)
Serum Prothrombin Activity.....	17.6 sec. (21)
Fibrinogen.....	149 mgms % (350)
Thrombin Time.....	40 sec. (14)
Platelets.....	120,000

was at the level of the ischial spines. An attempt was made to hasten delivery by application of Willet's scalp forceps. The procedure failed because of the friability of the premature fetus' scalp. After three grams of fibrinogen the values listed below were obtained:

Clotting Time	5 min.
Serum Prothrombin Activity	16.4 sec.
Fibrinogen	240 mgs. %
Thrombin Time	50 sec. (14)

The patient was given a fourth unit of blood, and throughout all the procedures remained in excellent condition.

In view of the fact that delivery could not be effected by Pitocin* stimulation or by attempts at scalp traction on the dead fetus, an immediate laparotomy was indicated. The blood picture was returning towards normal. An additional three grams of fibrinogen was given and the following blood picture was found:

Clotting Time	5 min.
Serum Prothrombin Activity	20.6 sec.
Fibrinogen	246 mgs. %

Under general anesthesia, with two units of blood being administered simultaneously, a laparotomy was performed. The peritoneal cavity contained 250 to 300 cc of bloody fluid. The uterus was extremely tense, firm and enlarged to the size of about a 36 week gestation. The peritoneal reflection of the bladder was elevated by bloody sub-serosal edema. The entire serosa of the uterus was intensely cyanotic, mottled and hemorrhagic. The uterus was delivered into abdominal incision and a total hysterectomy, with the fetus and placenta in situ was effected with relative ease. The patient tolerated the procedure very well and left the operating room in good condition.

Her post-operative course was entirely benign. The patient remained afebrile and had only a superficial right saphenous vein phlebitis which responded to ace bandages and mobilization. Coagulation studies on the second post-operative day revealed a complete return to normal.

Chairman King:

I will call on Dr. Martin Rosenthal, a member of the Hematology Department, who will discuss the entire subject of "Afribrinogenemia."

Discussion

Dr. Martin C. Rosenthal:

Hemorrhage during or following delivery has long been recognized as one of the major causes of maternal death or morbidity. As a general rule local uterine or placental factors have explained the majority of such cases, although it has long been suspected that in some, local factors were not adequate to explain either the severity of the bleeding or the widespread hemorrhagic manifestations. The recognition that a major coagulation defect exists in certain cases of pregnancy, has provided one of the most dramatic chapters in the history of obstetrics, and the newest science, if it can be called that, of coagulation.

No one who has witnessed such a case can help but be appalled at the speed with which an apparently routine delivery can be converted into a disaster. At one moment all is well, and the usual happy outcome is expected, and in the next instance the life of the mother and the baby are in jeopardy. How does such a situation develop?

At the present time, hypofibrinogenemia of pregnancy is recognized in association with five conditions of pregnancy, namely premature separation of the placenta, amniotic fluid embolization, some toxemias of pregnancy, criminal abortions, and intrauterine retention of the dead fetus. Without any doubt, the major cause of afibrinogenemia has been seen in association with premature separation of the placenta, as has been presented here tonight. The clinical picture is one of labor, which is accompanied by unexplained uterine bleeding, and symptoms associated with premature separation. Sometime during the course of the placental separation, it may be noted that bleeding seems more severe than can be explained by the clinical picture. In its severest form, multiple hemorrhagic phenomena develop and there occurs bleeding from venipuncture sites, from the gingiva as well as profuse vaginal bleeding.

If at this time a specimen of blood is drawn from the patient, it may not clot at all, or if it does clot, a tiny nub of fibrin is seen with many untrapped red cells. In some patients, even this clot which develops may rapidly disappear, leaving completely fluid blood in the test tube, and suggesting the process of fibrinolysis.

By this time, the patient is oozing from many sites, is in shock and may even be moribund. Reconstruction of the clinical sequence of events has led to the theory that the hyperfibrinogenemia, or in the severe patient, the afibrinogenemia, in premature separation, is due to intravascular coagulation of maternal blood with defibrination, as a consequence of the infusion of thromboplastic material. This thromboplastic material has been postulated to come from the placental site.

In premature separation of the placenta, the expanding hematoma which develops, has three roles in the production of this syndrome. First, by its expansion, it manages to extract from the placenta and other decidual elements, thromboplastic material. Secondly, in its dissection it exposes maternal uterine sinusoids, leaving the way open for thromboplastic material to infuse into the

maternal circulation. And finally, the expanding hematoma provides the necessary hydrostatic pressure to force the thromboplastic material into the maternal circulation.

Such intravascular coagulation, may be expected to deplete not only fibrinogen, but many other coagulation elements as well. Our own observations on the patients that we have studied, have revealed that in addition to a lack of fibrinogen, a deficiency of anti-hemophilic globulin, prothrombin, labile factor and platelets are found with a fair degree of regularity in these patients.

In effect, the fluid portion of the blood that circulates in these patients, is no longer plasma but is serum. Because of the observation of lysis of clot in some cases, it has been suggested by some of the workers in this field that the afibrinogenemia is not the result of defibrination, but possibly is the result of fibrinolysis.

The fibrinolytic system is a complicated system in which a plasma proteolytic enzyme, which exists in an inert form in all of us, is activated by a fibrinokinase present in many tissues. Under the influence of shock or trauma or hemorrhage, this fibrinokinase is released and profibrinolysin, (another name for this is plasminogen) is activated to fibrinolysin, an enzyme which attacks fibrin and fibrinogen, as well as some of the more labile components of the coagulation factors.

It is important to recognize that massive thromboplastin release or infusion directly brings about conversion of fibrinogen into fibrin, thus leading to afibrinogenemia. At the same time by producing shock, trauma and hemorrhage, this same event may also activate the fibrinolytic system, further depleting fibrinogen.

In amniotic fluid embolization, two pictures may develop. One is a picture of rapid shock, cyanosis and respiratory distress, with sudden death, so that no hemorrhagic phenomena may be encountered. Or else, the picture of afibrinogenemia may develop, usually accompanied by shock, quite out of proportion to the blood loss. In fatal cases, the typical findings are that of lanugo hairs, and fetal epithelium in the pulmonary vessels, and widespread intravascular deposition of fibrin, attesting to the acute defibrination that has occurred. The source of the thromboplastic material in this situation, seems to come directly from the amniotic fluid, and we have tested such amniotic fluid *in vitro* and have demonstrated considerable thromboplastic activity. Infusion of amniotic fluid into animals by various workers has produced a picture of defibrination not unlike that encountered clinically.

Afibrinogenemia, associated with a retained dead fetus, is seen most commonly in association with high titer RH isosensitization, but it is not confined to this condition, by any means. It is the one condition, of pregnancy associated with afibrinogenemia, that may come on gradually, so that detection is possible prior to the clinical advent of bleeding. However, in some patients even when followed carefully, the afibrinogenemia has come on with great rapidity in a manner quite analogous to that seen in other states.

The mode of removal of fibrinogen is not known in retention of the dead

fetus, although, as with the others, defibrination and lysis has been suggested. In the one patient that we studied quite carefully, a potent lysin was present, although by the time we started our studies, the patient had been in shock, so that shock may have been the cause of activation of the fibrinolytic mechanism.

The detection of hypofibrinogenemia, or afibrinogenemia, starts with an appreciation of its possible presence. Any unusual bleeding during pregnancy, or the suspicion of premature separation of the placenta, or the knowledge of a dead and retained fetus, should call for coagulation studies. Unfortunately, routine methods of fibrinogen determination take time, and time in many of these patients, is of the essence. As a rule it will take about one and a half to two hours to do the usual chemical estimations of fibrinogen.

Therefore, several rapid methods of fibrinogen estimation have been evolved, among them the Schneider Index, which is a dilution of the plasma to see the end points of clotting.

Figure 1 presents an example of the observations of the effect of the addition of thrombin to the plasma of a patient with afibrinogenemia. Before therapy was started, while the patient was actively bleeding, the addition of thrombin to the patient's plasma produced no visible clot. Following 200 ml. of blood, a

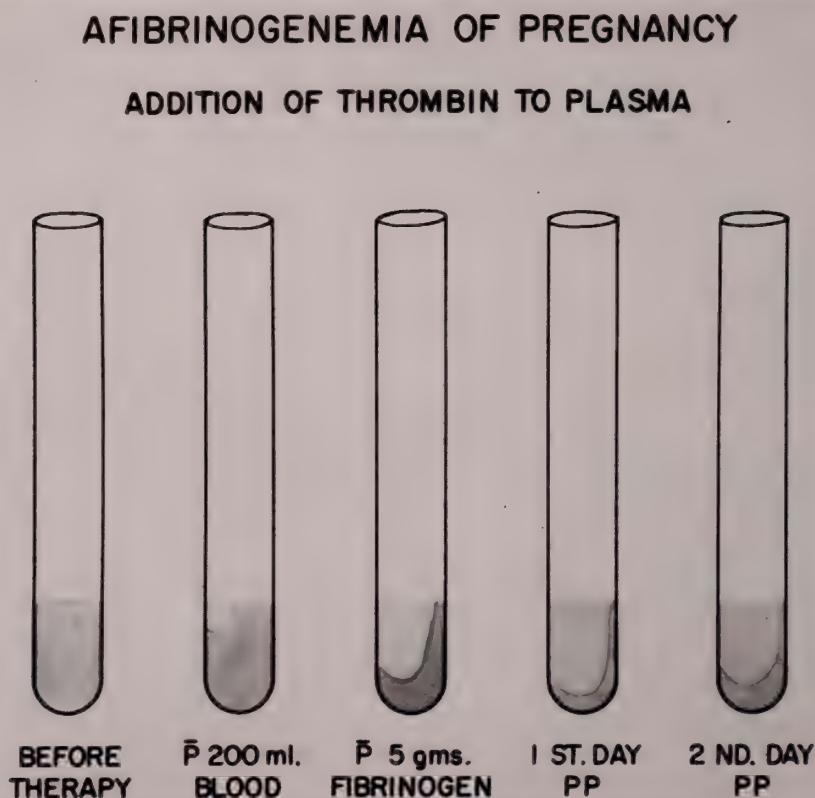


FIG. 1.

very tiny nub was first seen, and following five grams of fibrinogen, at which time clinical bleeding stopped, a larger amount of fibrin was noted. After this condition was terminated, the fibrinogen level swiftly restored itself to normal.

Of greater help, and certainly of more practical values, are observations on the clot itself. If the patient is suspected of afibrinogenemia, the simplest thing to do is to draw blood and put it in a test tube, and notice the type of clot. If the blood clots within a normal period of time, and then retracts to form a nice, solid clot with clear serum, or if, upon the addition of thrombin to freshly collected blood, a firm clot is formed, one can be reasonably certain that adequate fibrinogen is present.

On the other hand, if a clot is formed, which, when it retracts, retracts to a small nub with many untrapped red cells; or if, following retraction this clot dissolves, one either has hypofibrinogenemia, or else fibrinolysis, or both.

In total afibrinogenemia the blood will never clot, and thus will remain fluid. After a reasonable period of incubation, no clot will be noticed, and the cells will simply settle out of the fluid blood. When one adds thrombin to such blood, no fibrinogen is converted to thrombin because it is not present, and, therefore, this test which takes no more than about five seconds, will reveal total afibrinogenemia.

The therapy of this disorder is simple, but requires a good deal of coordination, and at the same time, rapidity in administration. The first thing that is necessary is the attack against shock, because shock, as mentioned before, will perpetuate the fibrinogen depletion. It is necessary to administer blood rapidly, and at the same time, if necessary, to give a pressor agent such as Levophed®.

Restoration of fibrinogen level can be brought about in very mild cases by the administration of whole blood. However, one pint of whole blood contains only about 750 milligrams of fibrinogen, and when the fibrinogen removal is rapid, this amount will be quite inadequate. Then too one cannot infuse whole blood fast enough to keep up with fibrinogen requirements. Therefore, it has been necessary to use concentrated fibrinogen preparations which fortunately are now in good supply. If a case is desperate, and no fibrinogen is available, it is a good thing to realize that concentrated dried plasma, not restored to its full volume, can provide a good source of fibrinogen, and has been used in the treatment of afibrinogenemia in Great Britain.

It is also necessary to restore the other depleted coagulation elements, and for this it is necessary to use the freshest whole blood possible. Once these measures have been brought about, it is necessary to consider ways in terminating the pregnancy, if this has not occurred spontaneously. With adequate control of the fibrinogen level, one can then think about rupturing membranes, or administering pitocin, or doing a hysterotomy, or even a hysterectomy. As you heard in the case presented this evening, it is possible, with adequate control through fibrinogen and blood, to perform a rather extensive procedure without jeopardizing the patient's life. Had this procedure been undertaken without any attempt to correct the fibrinogen lack, one would certainly have been in considerable difficulty, and the issue would have been in doubt.

Following the termination of pregnancy, usually one can expect a spontaneous

restoration of the fibrinogen in one or two days, although in some patients, if there has been any considerable period of shock, this may take as long as three or four days.

Occasionally, thrombocytopenia following afibrinogenemia, is somewhat of a problem. It may be related to the initial infusion of thromboplastic material, but not infrequently it is due to the rapid and multiple infusions of whole blood. However, usually five days after the episode is terminated, the platelet count comes up to normal, and no further difficulty is encountered.

In conclusion, I would like to pay tribute to Dr. Guttmacher and his staff, both the attending and the house staff, for their wonderful care of these patients. They really have done a magnificent job in recognizing this condition, and what's more, vigorously treating it, so that at times we are somewhat in the position of being the tail on the dog, and coming in after the situation has been very admirably handled by the Department of Obstetrics.

Chairman King:

The next entity is a rather common medical hazard of pregnancy, but you may have noted by Dr. Guttmacher's introductory remarks about the indications for a therapeutic abortion, that there has been a change in our appraisal of the relative gravity of this hazard. We seem to be less in awe of the risk involved, and this shift in attitude by itself makes it desirable that we present such a case here.

The case will be presented by Dr. Ira Gelb.

RHEUMATIC HEART DISEASE

Case Reports

Dr. Ira J. Gelb:

This evening I will present two cases which showed pertinent problems when they presented themselves in the Prenatal Cardiac Clinic. The first was a 25 year old gravida 3, para 2 Puerto Rican female. She was six months pregnant when seen for the first time on May 21, 1955 because a routine chest x-ray was reported to be consistent with the diagnosis of rheumatic heart disease. She denied any past history of heart disease and denied cardiac symptoms. Her past two pregnancies were completely normal.

When first seen, she had a regular pulse rate of 86 per minute and her blood pressure was 110/70. Her heart was not enlarged and the second pulmonic sound was louder than the second aortic sound. The first mitral sound was accentuated. There was a soft, grade one systolic murmur at the apex, and a grade two rumbling harsh presystolic murmur in the same area. A high pitched blowing diastolic murmur heard at third left intercostal space.

Fluoroscopic examination revealed a slightly enlarged right ventricle, an increased pulmonary artery segment, and a prominence of the pulmonary vascular markings. The electro-cardiogram was essentially normal except for some mild notching of the P waves. The diagnosis of rheumatic heart disease

and mitral stenosis was made. It was decided to treat this lady with prophylactic Bicillin® every two weeks.

The next time she was seen, she complained of fever, chest pain, and a six day history of white mucoid non-bloody sputum.

Physical and x-ray examinations at that time, revealed signs of bronchitis and possible early bronchopneumonia. She was admitted to the hospital as a precautionary measure. She remained in the hospital for nine days during which time she remained in bed and received penicillin.

When next seen in the clinic, she complained of severe shortness of breath, and an increase in weight of seven pounds in two weeks. She was given diuretics and improved.

On July 5, 1955, three weeks prior to expected date of confinement, she was prophylactically digitalised. Two weeks later the patient was hospitalized as a precautionary measure. On August 2, 1955, she had a normal, uncomplicated delivery. That same afternoon, she had a tubal ligation. This was also done without difficulty. She was seen again in the clinic after discharge, and until the present time is being maintained on digoxin and prophylactic penicillin.

The second patient presented a problem of whether or not a therapeutic abortion should be done during the first trimester of pregnancy. She was a 36 year old gravida 4, para 1 white female who was seen for the first time in the Prenatal Cardiac Clinic when she was three months pregnant. She stated that fifteen years ago a murmur was heard for the first time, although she denied any past history of rheumatic fever. Ten years ago she noted the onset of increasing fatigue and shortness of breath. Five years ago, she had an uncomplicated pregnancy. Between that time and 1952, she had a colectomy for acute colecystitis, and steroid therapy for ulcerative colitis.

On two occasions in the past three years, she stated that she had precordial and right shoulder pains at rest. Each pain had a duration of ten minutes and was associated with shortness of breath.

Therapeutic abortions were carried out after the first missed period in 1950, 1951 and 1953. Digitalis therapy was begun for the first time December 7, 1954 with a marked decrease in cardiac symptomatology. On December 21, 1954 she was admitted for the first time to The Mount Sinai Hospital for evaluation for indications for therapeutic abortion.

Physical examination revealed a pulse of 96 per minute and a blood pressure of 110/70. The heart was enlarged to two centimeters outside the mid-clavicular line in the fifth intercostal space. The second pulmonic sound was accentuated. The second mitral sound was very loud. She had also a Grade 3 harsh presystolic rumbling murmur at the apex, which radiated out to the left axilla. She had a very soft systolic murmur also at the apical area.

Fluoroscopic examination revealed moderate enlargement of the left auricle, and the main pulmonary artery, and increased pulmonary vasculature. The electrocardiogram showed notched P waves consistent with left auricular enlargement.

Included in the workup was a cardiac catheterization which revealed a pulmo-

nary capillary wedge pressure of 18 millimeters of mercury, a mean pulmonary artery pressure of 22, a pulmonary artery pressure of 29/5, and a right ventricular pressure of 42/5. Cardiac output both at rest and with exercise was completely within normal limits, and the circulation time was normal.

The diagnosis was rheumatic heart disease with mitral stenosis.

At this time several possibilities presented themselves. Should this lady, at this time, have a therapeutic abortion? Should she have a commissurotomy and be carried through to term. Should nothing be done now and she be carried through to term and then be evaluated for a mitral commissurotomy. It was decided to do the latter and she was seen at weekly intervals in the Prenatal Cardiac Clinic. Since she was allergic to penicillin, she was given tetracycline in addition to a low salt diet, diuretics and digoxin.

She continued to complain of mild symptoms of congestive heart failure. In addition, at the end of March, 1955, an active infiltrative lesion in the right apex was found, for which she was treated with INH and PAS. She was admitted for two weeks in May of 1955 and again July 2nd, 1955 because of vaginal bleeding. On the last admission the bleeding ceased within 24 hours, but it was decided to keep her in the hospital until the termination of her pregnancy. Her cardiac findings remained unchanged during her hospital stay.

On July 19, 1955, she had a normal, spontaneous delivery, and the patient was discharged to the Cardiac Clinic. Since that time she has been seen every two weeks and is now being considered for a mitral commissurotomy.

These two patients present important aspects in the treatment of cardiac disease during pregnancy. The first patient received prophylactic digitalis and was then admitted to the hospital. After a normal delivery, a tubal ligation was performed.

The second patient illustrated the problem of therapeutic abortion in early pregnancy and the various possible decisions.

Chairman King:

I will call on Dr. Simon Dack, one of our cardiologists, to close this conference by discussing rheumatic heart disease as a hazard of pregnancy.

Discussion

Dr. Simon Dack:

This part of the discussion of the "Medical Hazards of Pregnancy" may not be as exciting as the first two parts but it deals with the most frequent medical hazard in pregnancy. Therefore, a brief discussion of the problems involved in the prevention and management of cardiac complications in pregnancy would be timely.

Before reviewing the specific cardiac problems encountered in the two cases presented tonight, I would like to discuss very briefly the physiologic effects of pregnancy on the cardiovascular system in the normal woman. In the past few years, numerous studies, particularly of the cardiac output and intracardiac pressures, have been made in normal pregnant women and in those with rheu-

matic heart disease. In this hospital, as you know, a study was done in the Cardio-Pulmonary Laboratory.

I would like to show you three of the slides which they published in their paper. The first slide demonstrates the effect of pregnancy on the cardiac output. We all know that in normal pregnancy there is an increased load on the heart. This is the result of an increased cardiac output and increased blood volume. There is also increased blood velocity with rapid circulation time and the A-V oxygen difference decreases. However, the most prominent sign of the increased load on the heart is the increase in cardiac output, and in this slide we see the dramatic rise which begins at about the 16th week and reaches its peak usually between the 25th and 32nd week. Very few measurements have been done prior to the 16th week, because of the danger of x-ray exposure to the fetus. However, the average cardiac output of 6.5 liters per minute at the 16th week is definitely high and it continues to rise to a peak of 7 liters. Then by the 35th week it usually returns to normal. During the last four weeks of pregnancy the cardiac output is usually normal.

In the next slide it is seen that the pulmonary artery pressure may be slightly elevated. The mean pulmonary artery pressure, which normally averages between 10 and 15 mm., is normal at rest in most normal pregnant women, but after exercise it may rise to slightly elevated levels. Another important observation which was made in this study was the effect on the right ventricular diastolic pressure. Even in normal women, particularly in the middle trimester, the diastolic pressure of the right ventricle may be above 5 mm. Hg which is the upper limit of normal. Moreover, after exercise it may rise even higher to almost 10 mm. and this is the first physiological indication of heart failure. It is another indication of the increased load on the heart of the normal female during pregnancy. It is evident that in a patient who has antecedent heart disease, the physiological changes in the circulation which produce such an increased load on the heart may result in symptoms of congestive heart failure.

I would like to review briefly the principles of management of cardiac disease in pregnancy. Clinical observations in recent years have indicated that in a well-run prenatal cardiac clinic, or in private practice when patients are kept under close observation, the incidence of intractable or severe heart failure is very small. As a matter of fact, serious complications are most frequently observed in those patients who present themselves late in pregnancy and have not been adequately followed.

The principles which are important in the management of heart failure during pregnancy are the same as those applied to the management of heart disease in general, namely, the prevention and treatment of heart failure and the prevention and treatment of acute infections. The patient should be on a low calorie diet to avoid weight gain. The diet should be low in sodium in order to prevent accumulation of fluid. In our particular clinic population it may be difficult to impress the patient with the importance of salt and calory restriction, and many patients are given diuretics even though they may show no frank signs of heart failure. If they show evidence of excessive or too rapid weight gain, we do not

hesitate to use the mercurial diuretics in addition to oral diuretics such as Diamox® or Rolicton®.

Patients are digitalized if they have a large heart or if they show any signs of cardiac insufficiency. As Dr. Gelb mentioned, some patients are digitalized prophylactically, either in the middle trimester of pregnancy when the load on the heart is the greatest, or a week or two preceding the expected date of delivery. Of course, if digitalization is indicated in the early months of pregnancy, we digitalize slowly in order to avoid any aggravation of nausea and vomiting which may be present.

Pulmonary edema is a very serious complication of mitral stenosis during pregnancy. Fortunately, we have had very few patients with frank pulmonary edema, but in the cases reported in the literature the greatest number of deaths due to rheumatic heart disease in pregnancy has resulted from sudden intractable pulmonary edema. It usually occurs in the middle part of pregnancy when the load on the heart is the greatest. Treatment actually is a matter of prevention, that is, the early recognition and treatment of any signs of pulmonary congestion, such as increasing dyspnea, physical and x-ray signs of congestion, etc.

The recognition and treatment of anemia are a very important part of the treatment of heart failure. Firstly, the patient who has severe anemia may have symptoms and signs which simulate heart disease. In our clinic population in which nutritional anemia is so common, the patient may show systolic murmurs which are fairly loud and may simulate valvular heart disease. Also, tachycardia and overactive heart action develop. Such patients have often been erroneously diagnosed as having organic heart disease. Secondly, the patient with rheumatic heart disease who has a severe anemia may develop congestive failure early. There is an increased load on the circulation because anemia itself will produce a rapid circulation time, an overactive heart and an increased cardiac output and cardiac work. Such patients must be treated vigorously for the anemia in order to prevent the occurrence of congestive heart failure. We do not hesitate to give these patients transfusions, if we believe that the anemia may be causing or contributing to the congestive heart failure.

As I stated previously, the treatment of infections is very important because in patients with rheumatic heart disease the most frequent cause of heart failure is an acute infection. This applied especially to the first patient presented tonight. We did not hesitate to hospitalize her immediately at the first indications of an upper respiratory infection such as cough and signs of bronchitis. While the ordinary patient can be treated at home or on an ambulatory basis, such a patient should be admitted to the hospital and treated vigorously with antibiotics.

With regard to prophylaxis in patients who have rheumatic heart disease for the prevention of further attacks of rheumatic fever and of subacute bacterial endocarditis, this subject is still in a state of flux. Although we have given prophylactic treatment during the past four years, we do not have a fixed program as yet. It has been our policy that all patients with proven valvular disease

should be placed on prophylaxis, no matter what their age or how long ago their history of rheumatic fever goes back to. Since these patients report to the clinic at least once a month, we have decided to use intramuscular Bicillin* unless a known penicillin allergy is present. Patients who report at monthly intervals receive 1.2 million units. Those in the later periods of pregnancy come back every two weeks and they receive 600,000 units of bicillin. On this prophylactic regime during the past four years, we have had no instance of recurrent acute rheumatic fever, and only one instance of subacute bacterial endocarditis. This occurred post partum in a patient who had not been seen by us prior to labor, and therefore had not received prophylactic therapy.

What is the prognosis of patients with rheumatic heart disease who go through their pregnancy? Of course, it depends on the severity of the underlying heart disease, and on the management which they have been subjected to. Mild cases practically all do well, and mild cases rarely bring up the problem of therapeutic interruption of pregnancy. The pregnancy does not add any risk to their heart disease, if properly managed. Pregnancy in moderately advanced cases, as illustrated by the two cases presented tonight, does carry a definite risk. Heart failure may occur at any time in these patients, but with proper supervision as carried out in our clinic, practically all of them can be carried through without any complications.

The advanced group of cardiac patients, which is the smallest group, offers the largest number of problems. These patients develop signs of heart failure early in their pregnancy, and they require vigorous treatment throughout their pregnancy. In such cases, of course, pregnancy should have been avoided in the first place, and it is in this group in which therapeutic abortions are recommended. However, even in this group we have carried quite a few patients through to term without serious heart failure and they have delivered a viable baby. In some of these patients, of course, this is really more of a feat or tour de force rather than good medicine.

The age of the patient is important in prognosis. Most complications and deaths from heart disease in pregnancy have occurred in women over 35. The history with regard to previous pregnancies is important also. If the patient has gone through one or more previous pregnancies without any cardiac complications, the chances are that she will do well during the present one under proper management. However, it must be remembered that the patient's cardiac status may have deteriorated between pregnancies.

As far as the question of mitral valvulotomy is concerned, we have had very little experience in this hospital with valvulotomy during pregnancy. The question is still not settled. When valvulotomy was first introduced, most surgeons such as Brock, Harken, Glover and Bailey, recommended that selected patients of the type presented tonight, who have definite mitral stenosis and are seen in early pregnancy with signs of heart failure or incipient heart failure, should be subjected to a valvulotomy and carried through their pregnancy. Burwell, however, believed that valvulotomy should not be done during pregnancy, unless there was an emergency indication, such as intractable pulmonary edema. It

was his belief that it was difficult to evaluate the nature and severity of the mitral lesion during pregnancy. I have leaned to the latter view. We felt that such patients should have an interruption of their pregnancy if the heart failure was severe. If they can be carried through their pregnancy, then valvulotomy should be considered after pregnancy was terminated and the mitral lesion could be studied under more normal conditions.

Recently there has been an article in which there were reported 12 women who had mitral valvulotomies early in pregnancy for severe heart failure, and were carried through the rest of their pregnancy. All the patients lived and there was only one fetal death. So, there is still a difference of opinion. My own opinion is not fixed. I believe that if I should see a patient with advanced mitral stenosis who has evidence of pulmonary congestion or pulmonary edema which is not responding well to the usual therapy, and if it is early enough, the first or second trimester, I probably would advise that a mitral valvulotomy be performed.

In conclusion, I can't summarize better than by quoting the words of one of the pioneers in this field of heart disease, namely, Morgan Jones of England. First, he states, "as often as possible, allow pregnancy to pursue its normal course. But beware of pulmonary congestion and guard against heart failure, and especially watch for complications such as anemia and infection". Secondly, "if heart failure appears, treat it promptly and thoroughly". Thirdly, "avoid all modes of interference with labor unless there are obstetrical difficulties". And I should have stated that in our clinic we have learned from the obstetricians never to write on a chart, "Do a Cesarean", as the medical men used to do in the past. Cesarean sections are done only for obstetrical indications. And finally, "if any interference with pregnancy becomes essential, never permit it without first making every attempt to improve the cardiac condition first".

FRENCH INFLUENCES ON EARLY AMERICAN MEDICINE AND SURGERY

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American medicine and surgery found its origins in the 17th and 18th centuries. These two hundred years spanned an epoch marking one of those cyclic periods in the development of science and technology which have occurred at intervals since the beginning of historic time. Characteristically it began with an outburst of imagination and revolt, and ended with a clarification of its own accomplishments. Both phases of such an epoch have its good and bad points. One tends to admire most the initiative shown in the earlier phase, forgetting that along with the few great achievements are many which appear irresponsible. The second phase is that in which perhaps less imaginative but equally sound workers, trained in the newly acquired disciplines, measured and evaluated the offerings of their immediate predecessors and developed those which prove worthy into a workable body of knowledge.

The distinctiveness in the development of American medicine and surgery was conditioned by its origins within this stimulating and challenging epoch. Thinking was strong among the scholars of the 17th century, and aimed to be purely rational during the 18th. Tradition and authority did not carry the weight of previous centuries, they had been broken by the iconoclasts of the 16th. Men of vision felt free to develop their own thoughts, whether valid or not. Modern medicine had begun.

To the New World this intellectual freedom was an established fact. Where local authorities attempted to control it, their efforts were seldom successful outside a conservative in-group. At its start, the cultural aspect of the new settlements was truly primitive. Most activity was eclectic, few colonists were technically experienced beyond agriculture. Among the medical primitives of the 17th century colonies, the few qualified men were of course European trained, and seldom of the best quality. Most of what there was in the healing arts was conducted by part time, self-appointed, and, to a greater or lesser degree, self-read practitioners. By the latter half of the 18th century the most influential leaders of a now established profession in the cities and towns of the Atlantic seaboard had received at least part of their training in the principal medical centers of Europe, and the rank and file were physicians and surgeons trained by these leaders under an apprentice system, or at the newly created American medical schools.

Influences and directions cannot be gauged quantitatively. Among American medical and surgical practitioners of the first two centuries by far the greater part were poorly trained provincials who never entered into the stream of sci-

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tific or clinical progress. The gradual evolution of this rank and file into an efficient medical body was, as always, a product of the energy of its intellectual superiors. The influences which molded the leaders shaped the future of the profession in America.

That this influence was preponderantly English and Scottish cannot be controverted. The hospitals and lecturers of London and the University of Edinburgh stand far above all others in the credit column. However, very early in the work of American writers and teachers, it was evident that additional sources were being tapped. Among these were Dutch, French, German and Irish in approximately that order. Although London and Edinburgh were the great centers of medical training to the English speaking people of this period, a broader viewpoint of the contemporary western world allowed greater honors to Leyden and Paris, and perhaps to Montpellier. Scientific France of these two centuries is labelled with the names of Descartes, Lazare Riviere, Guy Patin and Jean Baptiste Denis, in the 17th, and Buffon, Laplace, Lavoisier, Nicolas Andry, Moreau, Chopart, Daniel Duhamel, Poupert, Winslow, Jean Louis Petit, Astruc, Pierre Dionis, Senac, and Vic d'Azyr in the 18th century. This galaxy of names provided a dynamic reservoir which drew both undergraduates and graduate students from all the known world.

Since Americans of the period who were able to travel abroad were congenitally English speaking, they of course, with few exceptions went to the English speaking centers. Their contacts with France were more apt to be those of a post-graduate nature seeking the critical overlay which marks the thinking professionals from the traditional. Therefore the relative time periods spent at Paris, Montpellier or Rheims as compared to the months or years of basic training at London or Edinburgh are not altogether a measure of their relative influences.

As in all modern historical analyses it is difficult if at all possible, to estimate values in terms of black and white. It is less dramatic but probably more sound to measure history in shades of gray. Many of these men made the Grand Tour, most starting by way of England or Scotland, then to Leyden, France, and an occasional visitor to Padua. Some took the tour in reverse, starting with Leyden or one of several French Universities. They returned home with varying views of the relative merits of each. Leaving out the English speaking sources to which they owed so much, most found it advantageous to go to Paris, some considered it a necessity, others preferred Leyden. However the generation which followed them and heard their lectures, went to Paris if it were at all possible to do so.

Early in this essay it was remarked that influences cannot be measured quantitatively. However historiography which is interpretive, must be based on factual material. The substance by which French influences on early American medicine and surgery may be estimated falls into three categories. These are, one, the number and professional importance of French physicians who came to the Colonies to settle and practice; two, the number of Americans who went to France to study or who included France in their graduate training; and three, the occurrence of French medical writings in native publications or libraries.

FRENCH PHYSICIANS AND SURGEONS IN THE COLONIES

In 1685 Louis XIV revoked the Edict of Nantes and thereby gave vent to the prosecution of French Protestants by the dominant Catholic party. As a result there followed an exodus of some of the soundest families of France. Among them were a number of physicians and surgeons one of whom, the Huguenot Pierre Ayrault settled in Rhode Island as early as 1686. Ayrault was one of the first qualified practitioners of record in that colony. In the same year another emigré, Giles Geodineau, arrived in New York, and Giles Mode and John Pettit came to the colony of Virginia. Four years later, Dr. Pinqueron joined Ayrault in Rhode Island. The influence of these four early Frenchmen, reaching from New England to the South greatly transcended their numerical paucity. They were among the very few University trained physicians in the Colonies at that time. Settled with large practices in their respective colonies, to a great extent they set the tone of medical conduct in their communities.

Out west, Jean Chapoton, born in Languedoc, arrived at the French post of Detroit in the mid 18th century. After the French and Indian Wars made it an English governed town, he remained as its principal and usually only practitioner until the time of his death in 1760.

During the Revolution several of the medical officers who came with the French troops and sailors remained to become leading practitioners in the last quarter of the century. Such was Joseph Phillipe Eugene Capelle, born in French Flanders. He arrived in the service of Rochambeau and de Grasse, was later attached to the headquarters of Lafayette. After the War he settled to practice in Delaware. He enjoyed a large personal practice and his position in the profession is best estimated by the fact that he was a prominent founder of the Delaware Medical Society. Pierre Chatard, born in the then French colony of Santo Domingo, educated in France, became an active physician in Baltimore.

Jean Francois Coste spent the latter years of the Revolutionary period in Virginia as Medical Director of the French Forces in America. His contact with the profession of that colony and state were sufficiently salutary as to have him invited to deliver a long remembered oration on medical matters at William and Mary College in Williamsburg before leaving the country. Jean Devese, has ever since been memorialized for his great effort when, while visiting in Philadelphia, he was caught in the professional and civic tumult of the great epidemic of 1793.

James Jerauld came to Massachusetts almost fifty years before the Revolution. Louis Mattel settled in South Carolina in the 1750's and became a prominent physician in Charleston, as did Norbert Vigneron in Newport, R.I. at about the same time. These names are but a part of the professional emigration, although a prominent part. As further records are searched, more and more appear who have been forgotten outside the older histories of their localities. Those mentioned, however, are sufficient to delineate a picture of French university trained doctors practicing in almost all the important cities of the Colonies from the last quarter of the 17th century through the Revolution and early Federalist period.

AMERICAN PHYSICIANS AND SURGEONS WITH FRENCH TRAINING

American colonials, who included France to a greater or lesser degree in their medical curriculum form a much larger and, especially in the 18th century, an even more effective force than did the French emigres. Among approximately one thousand practitioners of this period, at least fifty visited or were trained at French universities or hospitals. Fifty out of a thousand is indeed a small proportion. However these were obviously either the more privileged or more energetic of the students and their advanced training would inevitably be recognized on their return. In any professional group about ten per cent of its membership are generally conceded to hold positions of influence. The rest are usually followers. If this assumption is valid, it may be assumed that fifty out of one hundred or fifty per cent of the leadership of American medicine and surgery during its formative stage had come under some degree of French tutelage. This is indeed a large number.

The quantitative analysis can be carried even further when one considers some details of early American medical education. Most practitioners of the period received their entire training under the apprentice system. Even the best before 1765, the year of the founding of the Medical School of the College of Philadelphia, began their training under eminent doctors of their colony or state. Philadelphia, New York and Boston were the leading centers before 1800. By all standards their relative importance was in that order. Harvard, where until the latter part of the 18th century, interest was chiefly theological, had eminent names on its faculty, but not until some time after the beginning of the 19th century did it match the other two in scientific achievement.

Before the founding of the medical school in Philadelphia, John Redman (1723-1807) was the pre-eminent dean of the profession not only in that city, but along the central Atlantic seaboard. His early medical education with Doctor Kearsley was followed by a year of study in Edinburgh and London, the receipt of a doctorate from Leyden in 1748, and closed with a period in Paris. He is important to the subject at hand because among his own principal students was John Morgan, probably the greatest single figure in early American medical education. Morgan followed his teacher and went to Paris after receiving his doctorate in Edinburgh. His French period was important enough to gain him membership in the Academie Royale de Chirurgie. William Shippen Jr., and Benjamin Rush both of them Redman's proteges, included Paris in their post-graduate studies. A fourth Philadelphian of that period, Adam Kuhn, whose stature in botany and materia medica became international, received his doctorate from Edinburgh in 1767 after studying with Linnaeus in Upsala, and likewise finished at Paris. Redman became the first President of the Medical College of Philadelphia and the other four professors of the major faculties at the beginning or within a few years of its founding.

The Medical College of Philadelphia was the first medical school in the colonies and in the history of early American medical education its importance cannot be exaggerated. Its curriculum was distinctive, even adding one modern language

(French) as a prerequisite. The basic sciences were major items in its program. It exerted an immeasurable influence on subsequent teaching in the United States. Of course, Edinburgh and Leyden formed a major background for the first faculty, but its curriculum was not quite that of either of the two.

A steady stream of graduates continued to include France in their training. Among them was John Redman Coxe, Redman's grandson. Samuel Griffiths went from the University of Pennsylvania first to Montpellier, and then to London and Edinburgh. George Moore added a second doctorate at Edinburgh, and then went on to Paris. Jonas Preston was another. These Philadelphians were followed by others of like calibre, most of whom became active practitioners and teachers in the Middle and South Atlantic colonies and states.

The Medical School of King's College in New York, later to become Columbia University, was opened in 1767, two years after that of Philadelphia. Its original faculty contained six professorships. Of these the professor of surgery, John Jones had studied in London with William Hunter and Percival Pott, in Edinburgh and in Paris with Petit and Le Dran, after obtaining a doctorate from the University of Rheims. The surgical faculty at Columbia University therefore began with an American professor holding a French degree.

One of Boston's most prominent pioneers, Zabdiel Boylston, a physician trained under the apprentice system, but still a Member of the Royal Society of London, had spent time in the hospitals of Paris during 1721. Sylvester Gardner spent eight years of study in England and France before starting a large practice in Boston. Amos Holbrook, received most of his training in Paris.

To these names may be added several others of special note. Thomas Cadwallader, a founder of Pennsylvania Hospital, the Philadelphia Medical Society and the American Philosophical Society had studied with Cheselden in England and completed his studies at Rheims. Thomas and Phineas Bond returned to prominent practice and teaching in that city after a period in Europe which included hospital work in Paris. Lewis Johnson who practiced first in Georgia and later in New York City earned his "M.D." at Rheims in 1732. George Logan of Philadelphia, James McClurg of Williamsburg, Virginia, Benjamin Simons of Charleston, South Carolina, John Swett of Massachusetts, all of them personalities of note in early American professional life, had been for varying lengths of time, students or followers in the universities and hospitals of Paris, Montpellier or Rheims.

These physicians and surgeons held positions in early American medicine such that their personal impact in the profession, for good or evil, was inevitable. They reached from Portsmouth, New Hampshire in the North to Georgia and South Carolina in the South. A cosmopolitan background molded their practice. Through these men, to greater or lesser degree, the French component was transmitted to American medicine and surgery.

FRENCH MEDICAL LITERATURE IN AMERICAN LIBRARIES AND PUBLICATIONS

The third and last measurable factor in estimating French influences on early American professional life rests in the books to be found in libraries gathered by

teachers, and practitioners, and the representations of French written material in native journals. Again, one must acknowledge that the books of an English speaking professional community were preponderantly that of their own language. No attempt is being made to exalt the numerical value of French literature to be found among them. It suffices to discover that wherever library lists of institutions or prominent practitioners of this period can be found, important French representations are included.

The rather extensive medical library of John Crawford, who practiced in Baltimore during the latter half of the 18th century has been catalogued in a manuscript found in the library of the New York Academy of Medicine. Among the volumes listed are Charles Bonnet's, *Sur le corps organisées* in two volumes; an analytical essay on the faculties of the mind, and his treatise on entymology. Also included were the popular operative surgery, written by the great Parisian surgeon Pierre Dionis, and de Reamur's memoir on insects.

Benjamin Franklin's relations with the medical profession were intimate not only in the Colonies, but in Europe as well. His personal library included Bonnefoy's analysis of the reports of the French Royal Commission to study so-called animal magnetism, a pioneer attempt in psychiatry, Morand's catalogue of anatomical and surgical instruments used in the College of Medicine of St. Petersburg, and Gardanne's book on asphyxia.

The earliest catalogue available of the Massachusetts Medical Library was published in 1810. In it were listed many books dated before 1800 from earlier collections left to the library. Among these are found Baume's Pharmacopoeia, the standard reference book in pharmacy during the latter 18th century, both Dionis and Le Dran's books on operative surgery, Gardanne's Venereal Diseases, Petit's Diseases of Bones, and the 1783 volume of the French Journal of Military Medicine.

In the old Apothecary shop of restored Williamsburg in Virginia may be found the original bookshelf of the 18th century proprietor. It is a small collection of unimportant English and American herbals, but it contains one chief reference volume, the large Pharmacopoeia. It is of course Baume's.

A number of manuscripts have recently been acquired by the Rare Book Room of the Library of the New York Academy of Medicine. There are written documents, notarized, listing the personal properties of deceased New York physicians submitted for probate proceedings. That of Dr. Benjamin Lowe, "late surgeon and physician of the City of New York," died 1804, included the French Pharmacopoea of Baundereau. The book list of Dr. John Augustus Graham, died 1803, included Astruc's Treatise on Children, and that of Dr. James Church, died 1804, Pellerin's Venereal Maladies. These were book lists of active practitioners, not of great teachers, and still apparently required one or two French volumes to complete a well rounded personal shelf.

Before 1800 there were few native journals in which medical papers could be published. Only one was exclusively for the profession, the Medical Repository published in New York City. Volume I appeared in 1798; Volume II in 1799. The tables of contents of these two volumes are revealing in the number of French references included.

In Volume I, on page 204, is a translation of Foueroy's Remarks on a singular change in the human liver by putrefaction, translated from Volume III of the *Annales de Chemie* of Paris. On page 258 there appears an extract of a letter from Marsillac on small-pox vaccination translated from another French journal. Four other abstracts and news notes from French journals, societies, and book reviews also appear in this small volume. Volume II, 1799, contains a long article by Louis Valentin formerly of the French Forces Hospital in Virginia on small-pox inoculation. It also offers an announcement and description of the Medical Faculty of Montpellier, including discussions of the opinions of several of its professors on a variety of medical subjects. There are also printed several short reviews of recent French books.

There was no medical directory of the Colonies or the Federalist period so that names must be culled from local histories and memories. Toner's prodigious labors are the bible of personal references but here too a higher criticism must add and modify. Not all those listed as practitioners were fully so, a number appear to be no more than war-time regimental surgeon's assistants. However with each group of names added to the roster of early practitioners, the percentage of those with French contacts is maintained. In the same manner the more book lists or catalogues are uncovered, and these are quite difficult to come by, the more French references appear.

It is of interest that many of the teachers of England and Scotland with whom Americans studied had themselves been intimately associated with French sources. William Hunter, who spent some time in Paris quite proudly advertised that in his school of anatomy in London the latest French methods of dissection and the best French instruments were used. Cheselden was elected to the *Academie Royal de Chirurgie* of Paris. Sydenham is said to have studied for awhile at Montpellier. Nicolas Culpeper in the 17th century translated the French work of Riviere into English. William Petty, a pioneer in public health, studied at various colleges on the Continent, including Caen and Paris. Walter Harris of London, who wrote one of the early texts in pediatrics, lectured at the Royal College of Physicians and delivered several of the Harveian Lectures had earned his doctorate from the University of Bourges in 1675.

Here too the list increases with search. It would be impossible, even if it were profitable, to complete a listing of the names and references in any of the categories of evidence. Since the purpose of this essay is not to prove a predominance, but to demonstrate a significant French influence in the development of early American practice, enough has been described to maintain the thesis. In the upper echelon of teachers and practitioners, this influence permeated both directly and indirectly the education and literature of the 17th and 18th century native physician and surgeon.

DISCUSSION

Dr. S. R. Shapiro

I shall try to follow the pattern which Dr. Bick has outlined, that is, the three directions in which the French have influenced American Medicine.

The first deals with the French physicians who practiced in the colonies. By

an odd coincidence, several years ago, Mrs. Shapiro and I presented to the rare book collection of The New York Academy of Medicine, the manuscript of the elegiac poem on Dr. James Jerauld one of the outstanding French-American physicians of the Eighteenth Century. Jerauld was the type of man that Osler would have delighted in, the same type of man that he wrote about, Basset, the Alabama Student. He practiced in Medfield, Mass. for about thirty years (circa 1730-60). He was a man of really admirable stature and deserves much more attention than he has received. The *ELEGY*, a manuscript which was written by Nathaniel Fisher in the form of a letter to Jerauld's sister in 1769, showed how much he meant to the community, a point that Dr. Bick touched on.

As for the American physicians who were influenced by, or trained in the French Clinical Centers, the first one I would like to discuss for a bit is Dr. John Jones. Jones has the peculiar distinction of being the first American surgeon to practice lithotomy, which is primarily due to the fact that Jean Louis Petit, who dominated French surgery to 1750 was probably the leading lithotomist of his time. It is very doubtful that Jones studied with Petit, since Jones was 21 years old when Petit died in 1750 at the age of 76, but it is certain that he did study with Le Dran. Le Dran was sometimes referred to as the French William Hunter. He made the bulk of his rather large income by teaching anatomy, which was then the backbone of medical education. He had a large school which he set up at the Charité, and charged rather stiff fees, but taught so well that it was said that after you spent two years with Le Dran, you could literally dissect in the dark. Jones was the first professor of surgery in America, but it must be remembered that King's College, now Columbia University, did not have a genuine Medical Faculty until 1818, when the College of Physicians and Surgeons was established. Jones is probably best remembered today for being the author of the book that is most sought after by medical collectors of Eighteenth Century American origin, and that is his *Plain Practical Remarks on the Treatments of Wounds and Fractures* which he issued, very fortunately, in 1775, just as the Revolution was breaking out. Our friend, John Shaw Billings, says very tartly of this book that it contains a single original observation. I think that Billings may actually have been complimenting the book, since I know of a great many medical books that contain not a single original observation. In any event, there was a favorite anecdote of Fielding Garrison which he once narrated to my late father-in-law, Dr. Victor Robinson. Some of the blood which he had found on various copies of the first edition of Jones was in his opinion non-surgical blood, but the result of a fist colliding with a nose as two regimental surgeons fought for a copy since this was literally the only manual of surgery that the regimental surgeons had, and they needed it very badly.

Silvester Gardner, who was certainly one of the three or four best trained physicians in America before the Revolution, had the distinction of having been the richest physician in the Colonies before the war. However, Gardner, who spent at least two years in Paris, again at the Charité, bet on the wrong horse (he was a Tory), with the result that the bulk of his property, which, I might add, he did not make from medicine, but rather from such things as slave trading,

shipping, and smuggling, was confiscated by the Colony of Rhode Island. I have the manuscript petition which Gardner addressed very acidly to the legislature asking "why the devil they don't return us our property now that the War is over," and "why couldn't they let bygones be bygones," even if he had espoused the British cause. But I don't think that he got his money back.

I have here with me probably the two most interesting pieces done in the Eighteenth Century in America. One is the cornerstone of medical education in America, being John Morgan's *A Discourse Upon the Institution of Medical Schools in America*, Philadelphia, 1765. It occurred to me actually to read Morgan's book. I wonder how many have. I find much to my surprise that Dr. Morgan only refers to three sources in his footnotes in this entire work which is the "cornerstone" of medical education. Once he refers to Virgil in the well known phrase about "The road to Hell being a very smooth one," once to Horace, and the other time to the Academie Royale de Chirurgie, which shows how much he valued the *Memoires* of the Academie. In three places, he quotes material in extenso in French, and the only modern language which Dr. Morgan recommends to medical students as a "must" is French, although he does say that it would be wiser if they knew more Latin and Greek, which I daresay is still being said, and to very little avail.

The other piece is much more intrinsically valuable. This is the original manuscript notebook of the first American to receive the M.D. in America, John Archer, the first student of medicine to study in the College of Philadelphia, which is America's earliest medical school. He received his M.D. from John Morgan's hand, in 1767, so that this book of some 200 pages of manuscript notes, actually forms with Morgan's book the cornerstone of medical education in America. It is interesting to note that even when he refers to the American operators and venereologists, since those seem to be the two things that were most active in Philadelphia in those days, although I wonder how many of the descendants of the old families would like to hear this, the French influence was rather apparent, and I shall explain why in a little while. The influences best seen in America in the Eighteenth Century, first is lithotomy, probably due to the fact that there was so much calcium in the drinking water on the Atlantic seaboard, therefore stones in the bladder seem to have been quite prevalent. Dionis' famous *Cours D'Opérations de Chirurgie* in which he outlined in very great detail both the suprapubic and perineal approaches, was probably the most widely used surgical textbook in the first half of the Eighteenth Century. I have personally traced twenty-seven different editions, actually down to 1810, and when you consider that the work was published in 1707, that is quite startling. It was translated not only into all the European languages, but also into Turkish.

The other field, which I am sure will make Dr. Bick lick his chops, was orthopedics, mainly in the field of luxations and reductions. I believe, that the reason that orthopedics was so prominent was the fact that since the horse was the only method of transportation, and since most people, myself included, have never mastered the art of sitting on a horse, there must have been an awful lot of falls, resulting in dislocated or fractured bones.

Now to the influence of French literature on American Medicine. We have already spoken of Pierre Dionis and his *Cours D'Opérations de Chirurgie*. Dionis, oddly enough, was not attached to any hospital, but was attached to what we in America would call the zoo, the Jardin du Roi, where Buffon later was to do so much of his work. Dionis' lectures at the Jardin du Roi were actually on anatomy, and I am afraid they were mainly didactic, but his *Cours D'Opérations* first issued in 1707, still can interest us, if not for the surgical techniques, then for the wealth of anecdotes which can bring back the conditions as they existed in surgery at the end of the 17th Century and the beginning of the 18th Century. The last time I have seen it to have been advertised, was about 1810, which gives it a life span of 103 years, 25 times, I should say, that of a medical book today. The next one I should like to mention is Jean Louis Petit, whose dates are 1674 to 1750, and who wrote one book which was translated; his *Traité Des Maladies Des Os*, his book on the diseases of bones, published in 1723, which still flourished and was being offered by Collins and Perkins as late as 1811. He also wrote, over a long period, a work which was published posthumously, *Traité De Chirurgie Et Des Opérations*, published 24 years after his death and still used up to about the first quarter of the 19th Century. Petit is much more important than any of the French figures we have studied, primarily because he developed the so-called platform technique of amputation, which for the first time gave an actual working stump which could be used for prosthesis and traction, instead of a flat bare surface; he would carefully dissect out the muscles and fibers so that some sort of a leather and wood prosthesis could be erected on it. He is, of course, still remembered as the inventor of the screw tourniquet.

The next French figure we should know is the great benefactor of the female race, not only in Europe, but in America, and that is Jean Astruc. Astruc's fame as a gynecologist and venereologist has been somewhat over-shadowed in modern times by the fact that he was the founder of the higher criticism of the Bible in the 18th Century, but actually, his wonderful book, *Les Maladies Des Femmes*, was the bible of gynecologists of America. Practically any gynecologist of whom we have any record carried Astruc's work in the portable form that I have here. It is almost pocket size. It would make an interesting paper sometime to see why certain books are large and others are small. Astruc's work on syphilis and the use of the mercuric ointments, and his *Maladies Des Femmes*, I have seen in English translation as late as 1830, which again gives it a life of about 60 years. The next is the mentor of the men we were talking about, such as John Jones, John Morgan, and of our friend Silvester Gardner of the large income, and that is Henri François Le Dran, the preceptor of Anatomy at the Paris Charité. He was without question the leading teacher of Anatomy and Surgical Technique, and having served in many of the wars of the mid-century, he was the leading authority in Paris on military surgical intervention techniques. It is interesting to note that Albrecht Von Halle who so dominated medicine in Switzerland, was one of Le Dran's pupils as were, of course, Jones and Morgan. I note that as late as 1810 *Des Observations De Chirurgie and Des Opérations De Chirurgie* were both listed in Collins and Perkins catalogues as being available in an English

translation, which means that they had a life of nearly three-quarters of a century. The most important French surgeon from the standpoint of scientific achievement at the last half of the 18th Century, was undoubtedly Pierre Joseph Desault. After a period of service as the Surgeon at the Charité, he achieved what every French surgeon dreams of, I suppose all his life, namely, the post of Surgeon-in-Chief of the Hôtel Dieu, in 1788. Before Dupuytren who so dominated French surgery in the 19th Century, he had the largest surgical following of any surgeon on the continent of Europe. It is interesting to note that this not only held good for patients, of which he had some 10,000 in a single year, but also for students. I believe in one year he had students from about 16 countries, and considering the fact that travel in those days was far different from what it is today, this is quite a phenomenal thing. His *Journal De Chirurgie* (1791-92) was translated by Gosling into English and was issued in New York by our friends, Collins and Perkins, in 1810. His best work, that is, in printed form, is his work "*Fractures and Luxations*" which was translated by Caldwell and issued by Collins and Perkins, and was probably the most used work in orthopedies in America, up to about the time of Sir Astly Cooper, which is a generation later, and so it also had a life span, I should say, of about 40 years.

It is very interesting to note that the very first medical journal published in the United States, was a French journal, in origin. This was, and I give it first in its French version, *The Journal de Médecine Militaire*, publié par ordre du roi. This was a quarterly of which seven volumes were published from 1782 to 1788. This is not the first American medical journal, because it was purely French, but it was the first medical journal published in what is now the United States, published in New York, either in 1783 or in 1790, and it was published as *The Journal of The Practice of Medicine, Surgery, and Pharmacy in the Military Hospitals of France*, translated from the French by Joseph Brown, *Volume One*, 120 pages, and no other volume is known. This was probably issued as a trial balloon, and since the reception was probably notorious for lukewarmness, it was not continued, but it is interesting that the first journal of which there is any record in what is now the United States, should have been a literal translation of the French Military Medical Journal.

DYSPLASIA EPIPHYSEALIS HEMIMELICA (TARSO-EPIPHYSEAL ACLASIS)

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In 1950 a rare epiphyseal dysplasia involving one side of a single extremity was described by Trevor (1) who reported ten cases and gave the condition the name tarso-epiphyseal aclasis. Mouchet and Belot (2) had reported a single case in 1926 using the title "La Tarsomegalie." In 1953 Ingelrans and Lacheretz (3) published a case to which they gave the name "Chondrodystrophie Epiphysaire" and Donaldson *et al* (4) reported a case which they called "an osteochondroma of the distal femoral epiphysis." D'Angio, Ritvo and Ulin (5) in 1955 reviewed the clinical and roentgen manifestations of the condition and added another case. More recently Fairbank (6) collected 14 cases from various orthopedic centers in England and published an excellent review and analysis of these and 13 of the previously reported 14 cases. He considered the name tarso-epiphyseal aclasis unsatisfactory because although the tarsus is the most commonly affected site, it is not always involved and because the lesions are not necessarily confined to the lower limbs. In addition, the condition is considered to be a true dysplasia or abnormality of growth of the epiphysis and not a failure of the perichondrium to model the epiphysis as is implied by the use of the word aclasis. Since the condition affects only one side of an extremity he has proposed that the term hemimelica be added and suggests the title dysplasia epiphysealis hemimelica.

The disorder is probably a primary epiphyseal dysplasia involving the lateral or medial half of one or more epiphyses of a single extremity. In no case has more than one extremity been affected. The dysplastic epiphysis shows irregular enlargement of its affected side. In early cases this may be seen as numerous separate centers of ossification discrete from the main epiphysis or as a single outgrowth of mottled bone. With time these secondary centers tend to fuse with each other and later with the main body of the epiphysis. Usually the metaphyses are not affected but a few cases have shown widening of the regional metaphysis. Secondary deformity of an adjacent epiphysis or joint is common. Lengthening of long or short tubular bones has been described in a few cases. The most commonly involved sites are the talus and the lower femoral epiphysis. The upper end of the femur is rarely involved. When there are changes at the knee there are usually changes also at the ankle or in the tarsus. In several cases the navicular and first cuneiform of the foot have been affected and D'Angio *et al* demonstrated changes in the epiphyses of the proximal and distal phalanges of the first toe. Only two of the 28 cases reported have involved an upper extremity.

The following case is the third reported in the American literature and illustrates a metaphyseal finding not previously commented upon.

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

CASE REPORT

A 12-year old white male was admitted to The Mount Sinai Hospital because of a "swelling" on the outer aspect of his right ankle. The patient's mother had noticed that he was wearing out his right shoe more rapidly than his left. This had caused her to inspect his foot and ankle. He complained of no pain or disability and had been aware of the swelling for only two or three months prior to admission. Physical examination revealed a firm bony hard mass just below the right external malleolus. There was very minimal interference with all the motions of the foot except eversion which was significantly limited. The foot-print showed an accentuation of the lateral border of the right foot. The gait was normal. There were no other significant findings. Radiological examination of the right ankle showed an irregularly mineralized outgrowth from the infero-lateral aspect of the talus. (Figs. 1, 2.). The mass impinged upon the os calcis and tilted the tibio-talar joint upward on its outer side. (Fig. 3.). There was a small irregular outgrowth on the medial aspect of the distal fibular epiphysis and, in addition, a small bony exostosis arose from the medial aspect of the distal fibular metaphysis. (Fig. 4.). A skeletal survey showed no abnormalities of the other bones except three small outgrowths from the postero lateral aspect of the distal epiphysis of the right femur (Figs. 5, 6.).

Biopsy of the talar mass was reported as osteochondroma. Skeletal surveys of the mother and father showed no abnormalities.



FIG. 1. Antero-posterior view of the right posterior foot and ankle showing overgrowth of bone on lateral aspect of talus and tilting of the tibio-talar joint.

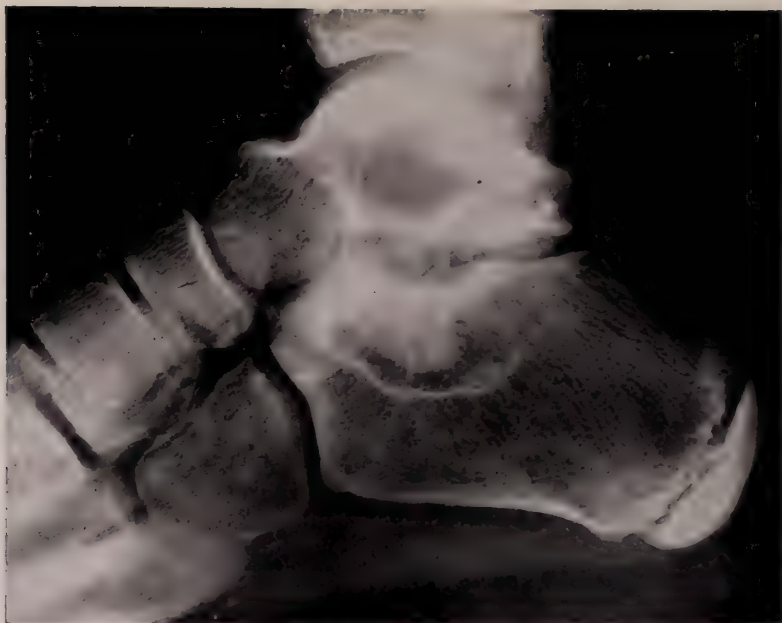


FIG. 2. Lateral projection showing bony overgrowth of talus with pressure defect on supero-lateral aspect of os calcis.



FIG. 3. Oblique projection showing large bony overgrowth of talus and pressure defect on os calcis. Irregular enlargement of medial portion of distal fibular epiphysis and exostosis arising from inner margin of fibular metaphysis.



FIG. 4. Oblique projection showing full extent of metaphyseal exostosis bordered by cortical bone and containing normal trabecular markings. Note overgrowth of fibular epiphysis on its medial aspect.

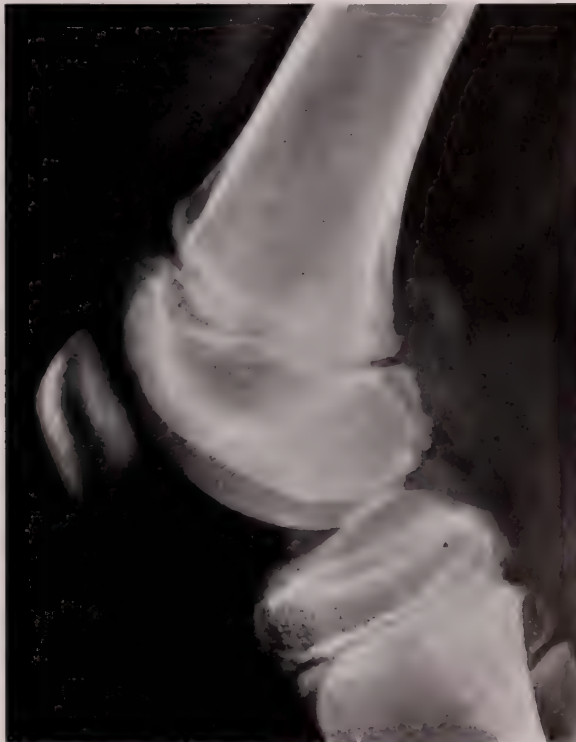


FIG. 5. Lateral projection of right knee showing irregular overgrowth of postero-lateral margin of distal femoral epiphysis.

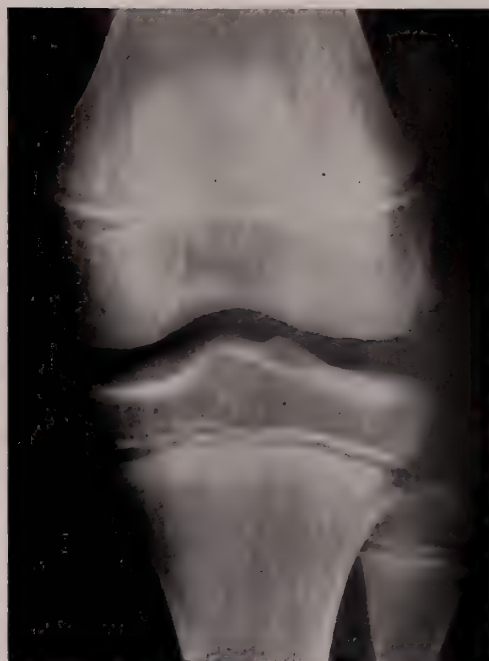


FIG. 6. Right knee showing irregular enlargement of postero-lateral margin of distal femoral epiphysis.

DISCUSSION

In two of the previously reported cases there has been widening of the femoral neck and in two cases marked widening of the lower fibular metaphysis. In two other cases for which roentgenograms have been published there have been exostoses from the metaphysis such as that demonstrated in this case. In Case 3 of Fairbank's series (6) the lesion is identical to the one reported here even to the site of involvement. Fairbank, however, made no comment regarding it. Ingelrans and Lacheretz (3) do mention an exostosis of the upper femur which occurred in their case. The demonstration of exostoses involving the affected extremities in at least three of the twenty-nine cases reported to date suggests that this may be an occasional feature of the condition.

The characteristic finding in dysplasia epiphysealis hemimelica is unilateral overgrowth of the affected epiphyses of a single limb. When more than one epiphysis is involved, which is usually the case, the abnormality is restricted to one side of the affected extremity. The condition is manifested clinically by the presence of a mass usually at the knee or ankle. There may be some interference with joint function but this is apt to be minimal. Pain is not common.

There have been no instances of the condition in the parents or siblings of the reported patients so that hereditary and familial influences do not appear to be significant. Only seven of the twenty-eight reported cases have been girls.

SUMMARY

1. A case of dysplasia epiphysealis hemimelica is reported. This is the third case reported in the American literature and the 29th case now recorded.

2. The condition is considered to be a primary epiphyseal dysplasia which characteristically involves the lateral or medial side of a single extremity. In this case the lesions involved the lateral side of the right foot, ankle and knee.

3. Metaphyseal exostoses have been demonstrated in at least three of the 29 reported cases and constitute a possible feature of the affection upon which there has been no previous comment.

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NOTE: Since this paper was accepted for publication another case has been reported in the American literature. KEATS, T. E.: Dysplasia Epiphysealis Hemimelica. *Radiology* 68: 558, 1957.

EFFECT OF ORINASE (1-BUTYL-3-PARA-TOLUENE SULFONYLUREA) ON ADRENAL RESPONSE TO CORTICOTROPIN

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AND

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It has been reported (1, 2, 3, 4) that adrenal cortical activity remains unaltered in the human subject following the administration of Orinase. Adrenal cortical functions in the reported studies were determined by the daily urinary excretion of the neutral 17-ketosteroids and 17-hydroxycorticoids.

The present report is concerned with the responsiveness of the human adrenal cortex to stimulation with corticotropin before and after the administration of Orinase.

MATERIAL AND METHODS

Five hospitalized subjects, including one with diabetes mellitus (S. J.), were studied. None showed any evidence of adrenal cortical inadequacy. All patients were maintained on a regular hospital diet throughout the period of study.

Following a two day control period, ACTH-Gel was given for two days in a daily dosage of 80 units administered intramuscularly in two divided doses. From the fifth to the tenth day inclusive 3 gms of Orinase‡ were administered in a single oral dose each morning. On the last two days of the administration of Orinase, ACTH-Gel was again given in a dosage of 80 units administered intramuscularly in two divided doses. In one subject (F. E.), the administration of Orinase was continued for six more days in a daily dosage of 4 gms.

Throughout the study the urine was pooled in 48 hour samples and the excretion of the neutral 17-ketosteroids and 17-hydroxycorticoids measured. Prior to the first injection of corticotropin and two hours thereafter, blood was drawn for determination of plasma 17-hydroxycorticoids (5). The latter test was carried out also on the fifth day of the administration of Orinase. The 17-hydroxycorticoids in plasma and urine were determined by the method of Porter and Silber (6), and the neutral 17-ketosteroids by the method of Holtorff and Koch (7).

RESULTS

The results are summarized in Figure 1. The data do not show any consistent effect of Orinase on the plasma levels of the 17-hydroxycorticoids following the

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* This work was aided by a fellowship from the Dazian Foundation for Medical Research

† Trainee, U. S. Public Health Service

‡ Kindly supplied by the Upjohn Company, Kalamazoo, Michigan

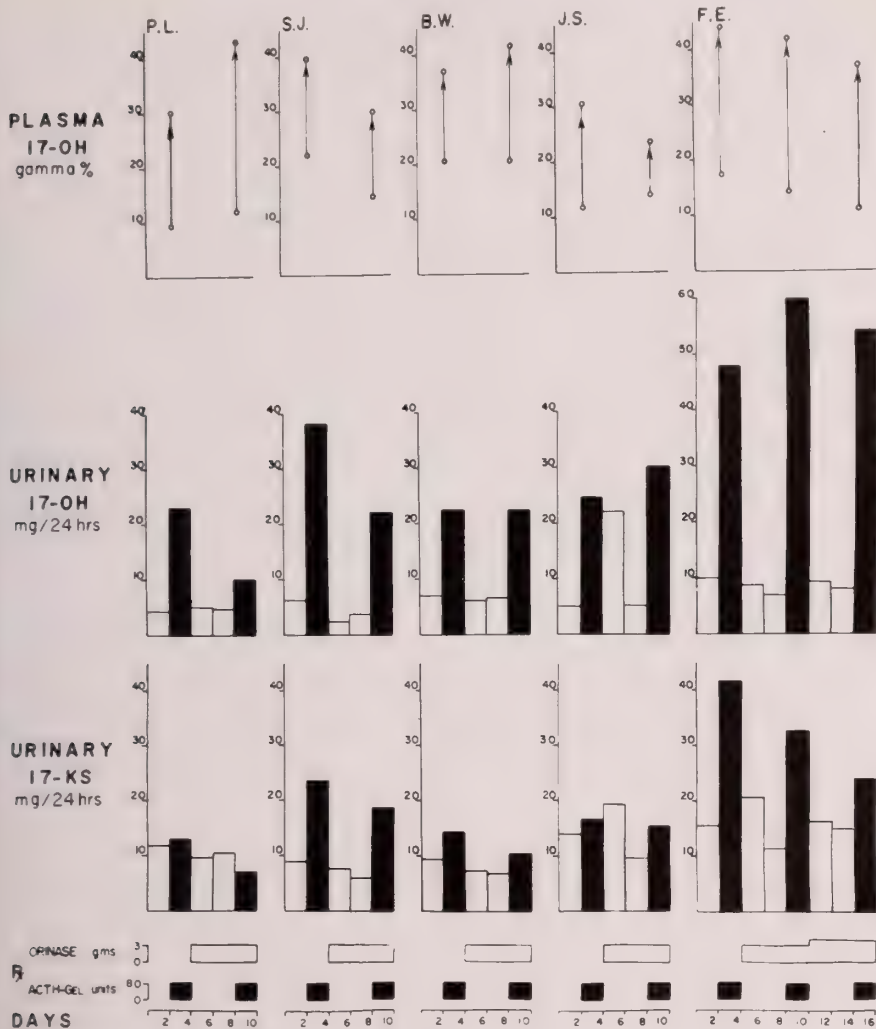


FIG. 1.

administration of corticotropin. Nor does Orinase alone cause any change in the urinary excretion of either the 17-hydroxycorticoids or the neutral 17-ketosteroids, as compared to the control period. When the effects of the administration of corticotropin on the urinary excretion of the 17-hydroxycorticoids during the Orinase and control periods are compared, the following results are noted: During the period of Orinase administration the urinary excretion of the 17-hydroxycorticoids was decreased in two subjects (P. L. and S. J.), unaltered in one (B. W.), and slightly increased in two (J. S. and F. E.). In all subjects the urinary excretion of the neutral 17-ketosteroids was slightly decreased during administration of Orinase. In patient F. E., who was given Orinase for six more days in a daily dosage of 4 gms, the reduction of the urinary excretion of the neutral 17-ketosteroids was more pronounced.

Summary

1) Orinase did not cause consistent changes in the levels of plasma and urinary 17-hydroxycorticoids following adrenal cortical stimulation with corticotropin.

2) There did occur a smaller increase in the urinary excretion of the neutral 17-ketosteroids following the administration of corticotropin, while the patients were receiving Orinase, as contrasted to that observed during the control period.

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COLPOMICROSCOPY

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AND

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The purpose of this report is to present our experiences and acquaint the medical profession with an instrument that is relatively new and little known in this country. It has potential value as an aid in the study of lesions of the cervix with particular reference to the diagnosis of carcinoma.

The colpomicroscope* should not be confused with the colposcope which reveals a slightly magnified view ($10-20\times$) of the cervix and which was introduced in 1925 by Hinselmann (1). Interest in this instrument has been revived recently in this country (2, 3).

Colpomicroscopy is the direct visualization of the cervix under sufficient magnification to yield microscopic cellular detail *in vivo*. The colpomicroscope was introduced by Antoine in 1949 (4). In the past few years it has been used in several German and French gynecologic clinics (5-10).

This instrument has an external light source which transmits light through the microscopic tube around the optical system in the shape of a hollow cone with a focal point just beyond a plane optical glass covering the front of the shielding guide tube (Fig. 1). This tube covers the microscope and is fixed to it (Fig. 2). The illumination thus provided is indirectly reflected from the surface of the cervix. This shielding guide tube can be easily detached, cleansed, and sterilized by immersion in aqueous Zephiran® 1:1000 for thirty minutes. The front glass plate of this tube must adhere to the moist surface of the cervix to produce a flat field. There are two controls, a vertical and a horizontal, which moves this protecting tube to cover a visible area of 65 square millimeters. Magnifications of $175\times$ to $280\times$ are obtained, depending on the ocular lens used. A small micrometer screw is used for focusing.

Cytologic visualization can only be accomplished after staining of the cervix. A special hematoxylin stain† is used routinely by placing over the cervix for three to five minutes a swab of cotton saturated with the staining solution. (Aqueous toluidine blue (1%) stains quicker and can also be used.) Visualization through the colpomicroscope is depicted by the photomicrographs (Fig. 3-5). The depth of visualization is stated to be 0.7 mm. The nuclei of some of the deeper unstained cells can be visualized by focusing through the superficial layers.

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* Mfd. by Reichert, Vienna. Available in U. S. A. from Wm. J. Hacker & Co., Inc., 82 Beaver St., New York 5, N. Y.

† One gram hematoxylin, 0.2 grams sodium iodate, 50 grams potassium aluminum sulfate is dissolved in 1 liter of distilled water. Fifty grams chloral hydrate and 1 gram citric acid is then added.



FIG. 1. Diagram showing the optics and illuminating system in the colpomicroscope.



FIG. 2. The colpomicroscope Model II.

Experience with this instrument in 48 cases covering the cervixes of normal pregnancy, erosion, and carcinoma, reveals certain advantages and disadvantages. The advantages are:

1. Visualization of living cells under microscopic magnification in situ by frequent painless examinations;

2. Neoplastic lesions of the cervix can be readily visualized from the squamous columnar junction outward;

3. This technique introduces many potential areas of investigation and becomes a research tool for studying cervical cytology in situ as a reflection of

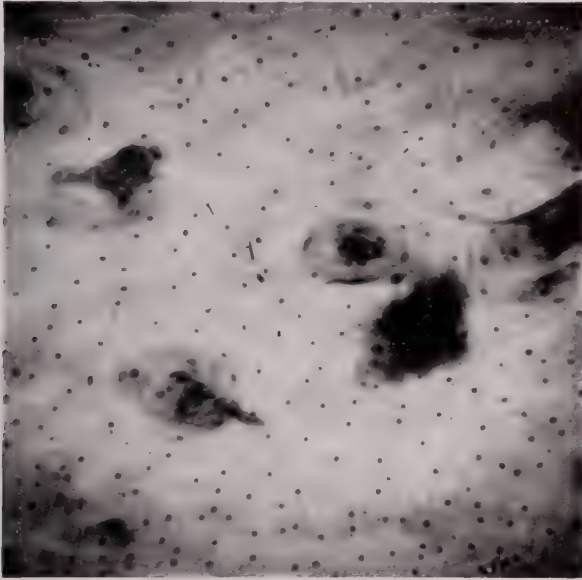


FIG. 3. Photographs of the squamous cells of the cervix uteri as seen through the colpomicroscope $\times 525$. 12th day of a 29 day menstrual cycle.



FIG. 4. Photomicrograph of the cells of the cervix uteri 10 weeks gestation $\times 525$. The nuclei are pale staining and crowded.

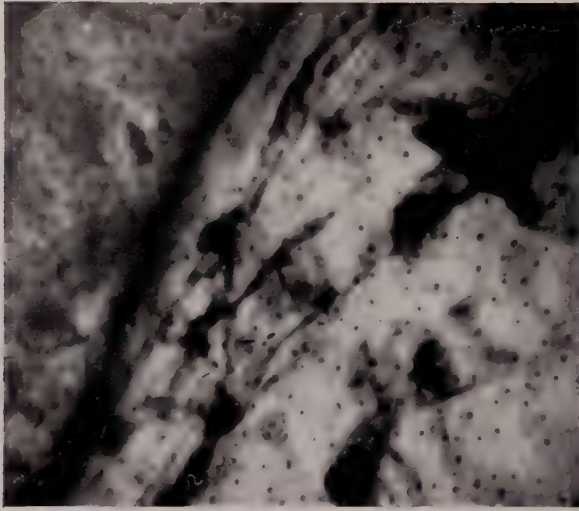


FIG. 5. Photomicrograph of the cervix at the edge of a carcinomatous ulcer at the left with normal squamous epithelial cells to the right. The diagonal linear markings are due to mucosal folds $\times 525$.

hormonal changes in the menstrual cycle, in pregnancy, in atypical epithelial states of the cervix and questionable Papanicolaou smears.

The disadvantages are:

1. One cannot visualize the surface of the endocervical canal, thereby eliminating the usefulness of this instrument in diagnosing cancer of the cervix originating in this location;
2. Invasive malignancy cannot be unmistakably diagnosed as such, and must be confirmed by biopsy;
3. Early in situ carcinoma that may start deeper in the epithelial layers and which has not broken through the surface, would not be seen by this instrument;
4. If there is active bleeding or necrosis of the cervix, cytologic detail is obscured.

The colpomicroscope was not devised to replace Papanicolaou smears or biopsy of the cervix, but to supplement these two procedures by a new technique which may increase the efficiency of early diagnosis of cancer of the cervix. This was demonstrated by Antoine (11).

In the unstained cervix, surface capillaries are visible, revealing various networks with the red blood cells visibly flowing through them. Changes in the vascular pattern occurs with hormonal phase changes and in pathologic states.

COLPOMICROSCOPIC PHOTOGRAPHY

There was no over-volting device available for photography for the older Model I which was used in this series. This device increases the light by three to four fold for a short duration.

Model II which was used for a short period of time is the more desirable in

strument and a definite improvement over Model I in that it is much easier to handle and the light source has been moved toward the rear of the instrument which eliminated the discomfort of the heat from Model I.

The photographs were taken with a Kine Exacta camera with a green filter using Tri-X Panchromatic Eastman Kodak film at 1/5 second exposure, developed in Microdal (Kodak) 68° F. for twenty minutes. Good color photographs were obtained with the over-volting device which requires 1/10 to 1/5 second exposure using flash Anscochrome or Ektochrome film.

SUMMARY

A brief description and our experience with the colpomicroscope are presented. This instrument has many possibilities as an investigative and diagnostic tool for the study of lesions of the cervix uteri.

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Radiological Notes

CASE NO. 18

A nine year old girl was admitted with a history of vomiting of mucoid material, epigastric pain and anorexia for nine days. These symptoms appeared after attending a birthday party. A local physician discovered a hard, moveable mass about 7 x 5 cm in the epigastrium and the left upper quadrant.

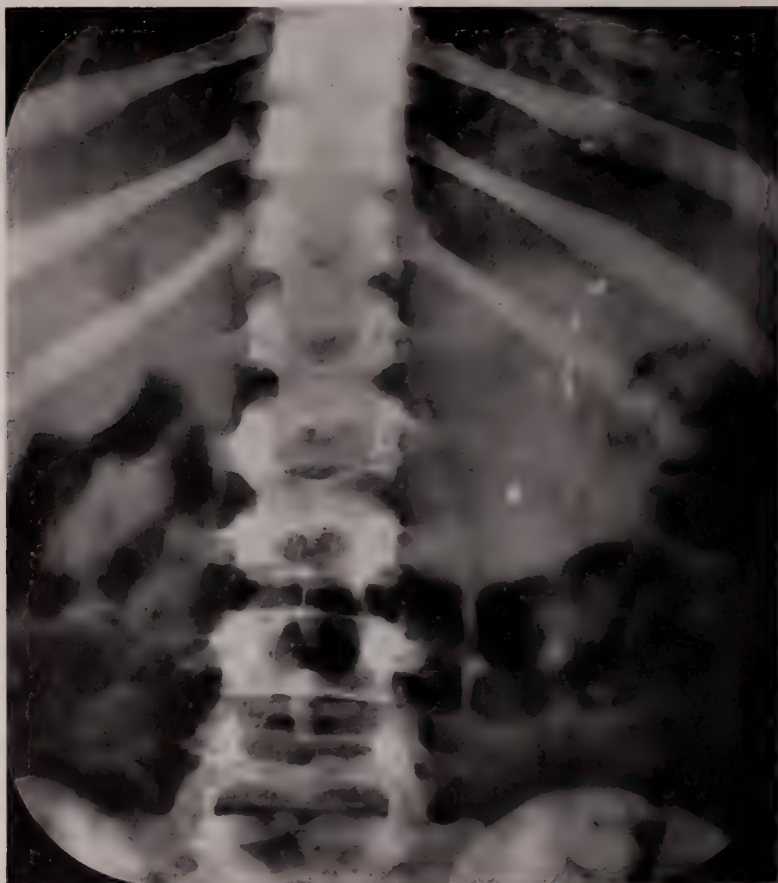


FIG. 1. Simple film of the abdomen shows scattered multiple discrete densities of varying shape high on the left side. They are unusually dense, homogeneous and several appear to be linear in configuration. There is also evidence of a diffuse increase in density in the left upper quadrant, but no definite borders of a soft tissue mass can be discerned.

Roentgen examination of the abdomen (Figs. 1, 2) showed multiple scattered sharply demarcated opacities located anteriorly in the left upper quadrant which maintained their positions relative to each other. Because of the physical find-



FIG. 2. Lateral view of the abdomen demonstrates that the scattered densities are located anteriorly. They appear to maintain their positions relative to each other.

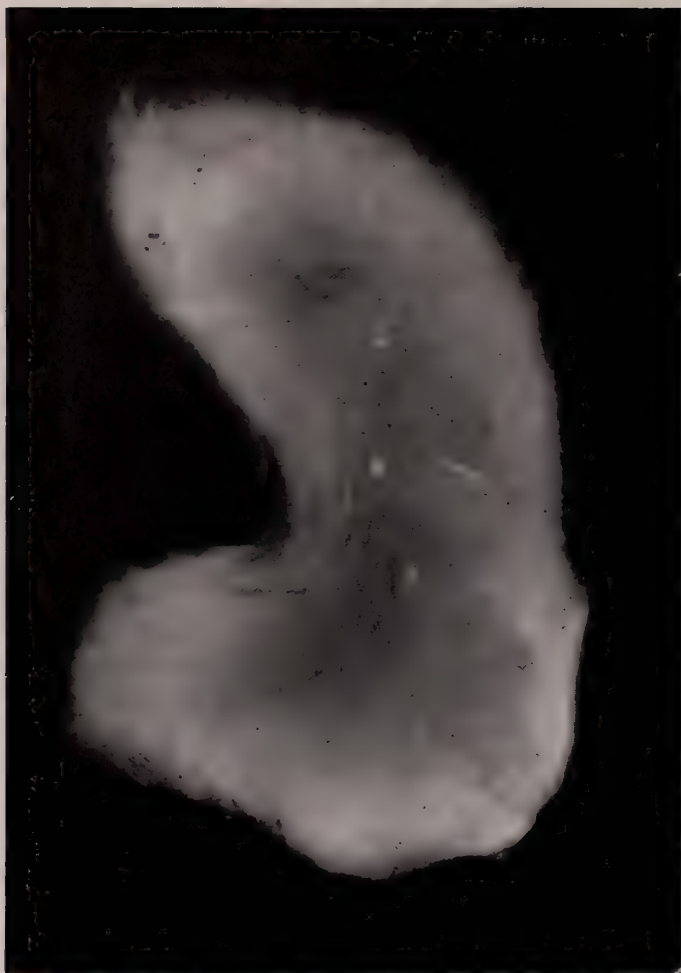


FIG. 3. Roentgenogram of trichobezoar removed from the stomach shows metallic foreign bodies enmeshed within the hair ball.

ings, the preoperative impression was a tumor of the left lobe of the liver. At exploration, a large hair ball, filling the body of the stomach and extending into the antrum, was removed by gastrotomy (Fig. 3). Subsequent questioning revealed hair swallowing since the age of two.

Final diagnosis: Trichobezoar with enmeshed metallic foreign bodies.

CASE NO. 19

A 20 month old female child was admitted with a history of meningitis which had recurred three times in a period of five months. The child had been hospitalized at two different hospitals during these previous episodes. As far as could be determined, the meningitis was pyogenic in nature, although culture reports were not available. Smears of spinal fluid during the second episode were said to

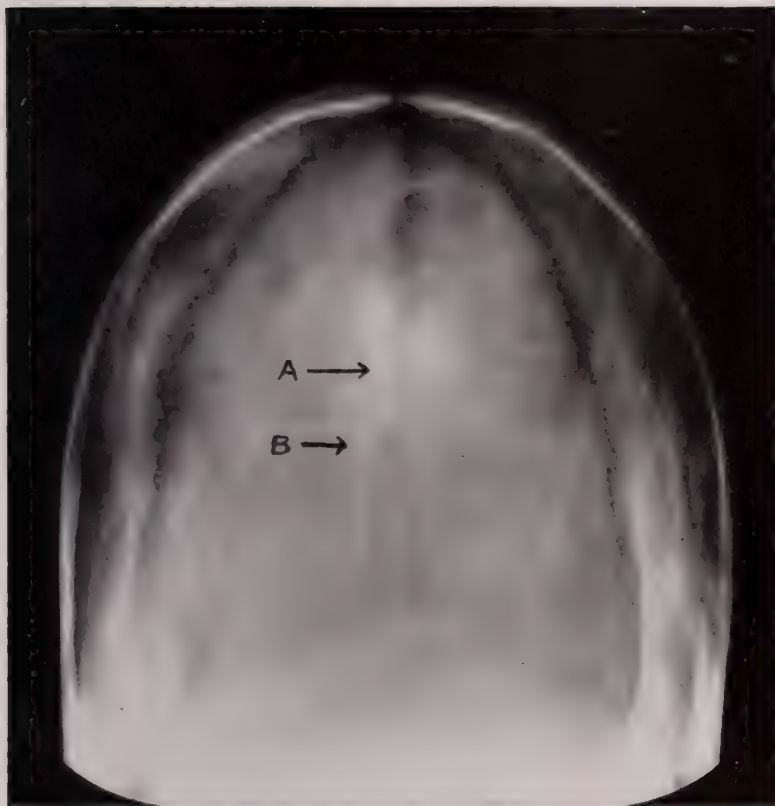


FIG. 1. Towne's view of the posterior fossa shows a lucent canal (A) in the midline, 2 mm. in width, with straight parallel borders. This canal transverses the occipital bone about 4 cm. below the lambda and enters a depression or fossa (B) demarcated superiorly by a dense crescentic line with an ovoid area of relative lucency below it.

have shown gram-negative diplococci. In the week prior to admission to this hospital, there had been headache, listlessness, vomiting, an unsteady gait, fever and leucocytosis. Physical examination showed evidence of meningitis which was confirmed by spinal tap. Culture of the spinal fluid yielded staphylococcus aureus. In addition, however, a round indurated erythematous area was present in the midline of the occipital region just above the external occipital protuberance. A small dimple was noted in the center of this area. Questioning revealed that this occipital mass had been present from birth and had drained milky fluid on occasion.

Roentgen examination of the skull (Figs. 1, 2, 3) showed a short canal in the midline of the occipital bone which ended into an ovoid depression of the inner table.

The diagnosis of a dermoid cyst of the posterior fossa joined to the skin of the occipital region by a stalk traversing the calvarium was made. At exploration, this was confirmed. A cyst about 2 cm in diameter was found in the midline displacing the vermis upward, the cerebellar hemispheres laterally, and the

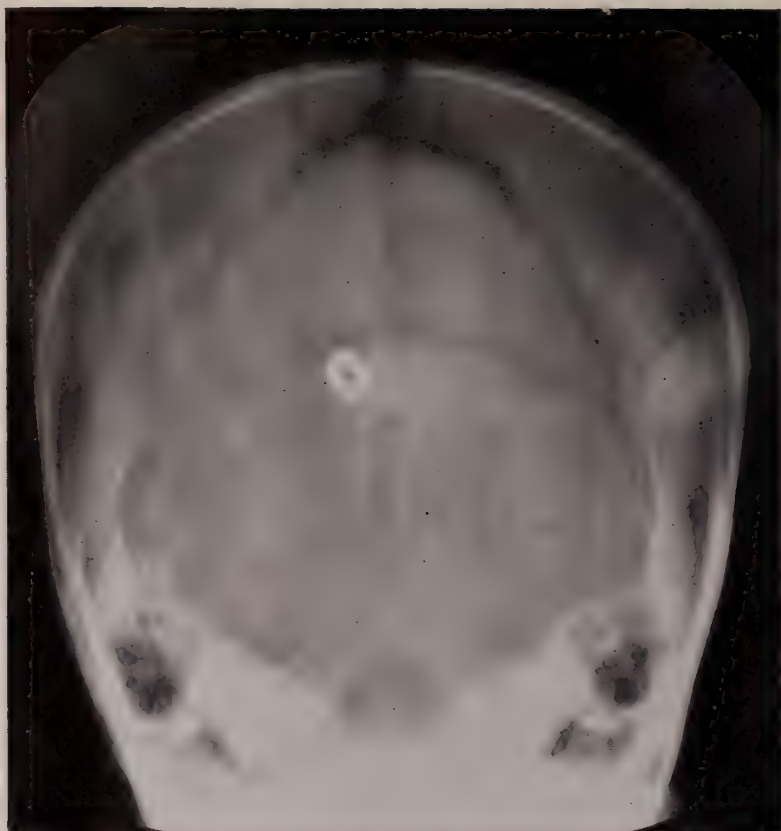


FIG. 2. Towne's view of the posterior fossa with an opaque marker adjacent to the external draining sinus. Features are similar to Fig. 1; the opaque marker is located adjacent to the bony canal.

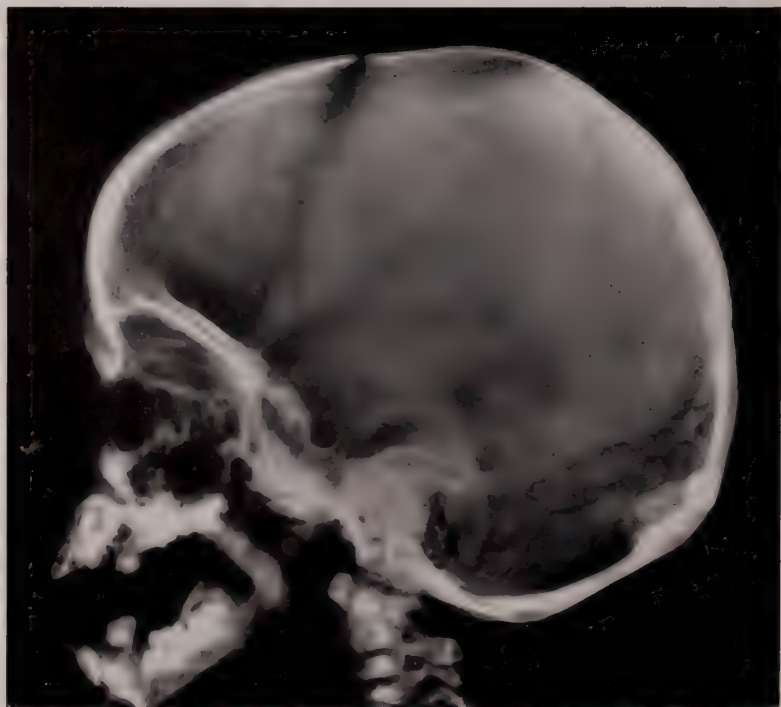


FIG. 3. Lateral view of the skull with an opaque marker adjacent to the external sinus track in the occipital region. The bony canal is faintly seen below the marker. (The overlying soft tissue density is an artefact due to immobilization.)

cerebellar tonsils downward. The cyst was removed, including a fibrous stalk which connected it to the skin dimple over the occipital bone. Opening of the cyst revealed yellowish, gruel-like material with numerous hairs. On microscopic section, a thin sinusoidal structure was seen to extend along the long axis of the stalk.

Post-operatively, hydrocephalus became progressive. A ventriculo-pleura communication was created, but patient continued to go downhill and succumbed three months after admission.

Final diagnosis: Intracranial posterior fossa dermoid cyst.

CASE NO. 20

Submitted by

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AND

JOAN ELIASOPH, M.D.

Apart from fistulous communications between the sigmoid and the small intestine, radiographic alterations in the sigmoid in regional enteritis are extremely uncommon. The roentgen findings in the sigmoid, when viewed alone, can be perplexing and the nature of the underlying pathological changes may be obscure. They may be confused with carcinoma or diverticulitis. A small intestinal series in this situation may clarify the problem. The following is the report of the roentgen evaluation of such a case.

A 45 year old man was referred for barium enema examination because of lower abdominal pain. He gave no past history of pertinent illnesses or surgical procedures.

On barium enema, in the midsigmoid (Figs. 1A, 1B), there was a 5 6 cm. segment of limited distensibility which offered no obstruction to the flow of barium. The caliber of the lumen varied slightly during the course of the study. On the superior wall, there was a suggestion of a small scalloped defect. The mucosa was intact and no intraluminal masses were seen. No diverticula were identified and there was no extraluminal barium. The remainder of the large intestine was normal.

The nature of the lesion in the sigmoid could not be determined from the roentgen study. It was not characteristic of either diverticulitis or carcinoma.

A small intestinal study had been performed previously at another institution and there was a question of an abnormality in the small intestine. Accordingly, the study was repeated. The terminal one foot of ileum was demonstrated to be involved by regional enteritis manifested by marked narrowing and spasm of the bowel lumen, mucosal ulcerations and inflammatory polyps (Fig. 2). No fistulas were seen. The involved bowel segment was markedly separated from adjacent bowel loops due to thickening of the bowel wall and intervening mesentery. The proximal portion of the involved ileum was situated in close relationship to the sigmoid with an intervening distance of 1-2 cm. The proximal ileum and jejunum were normal.



FIG. 1A

FIG. 1A. Spot film of the sigmoid: There is a short segment of limited distensibility in the midsigmoid with coarse spiculation of the contours and a suggestion of a scalloped defect on the superior wall. The mucosa is intact. There is no obstruction. No extraluminal barium is seen.



FIG. 1B

FIG. 1B. Spot film of the sigmoid: In a more oblique projection, the bowel lumen appears more distensible. The prominent mucosal folds are again seen along the bowel contours. No diverticula are noted.

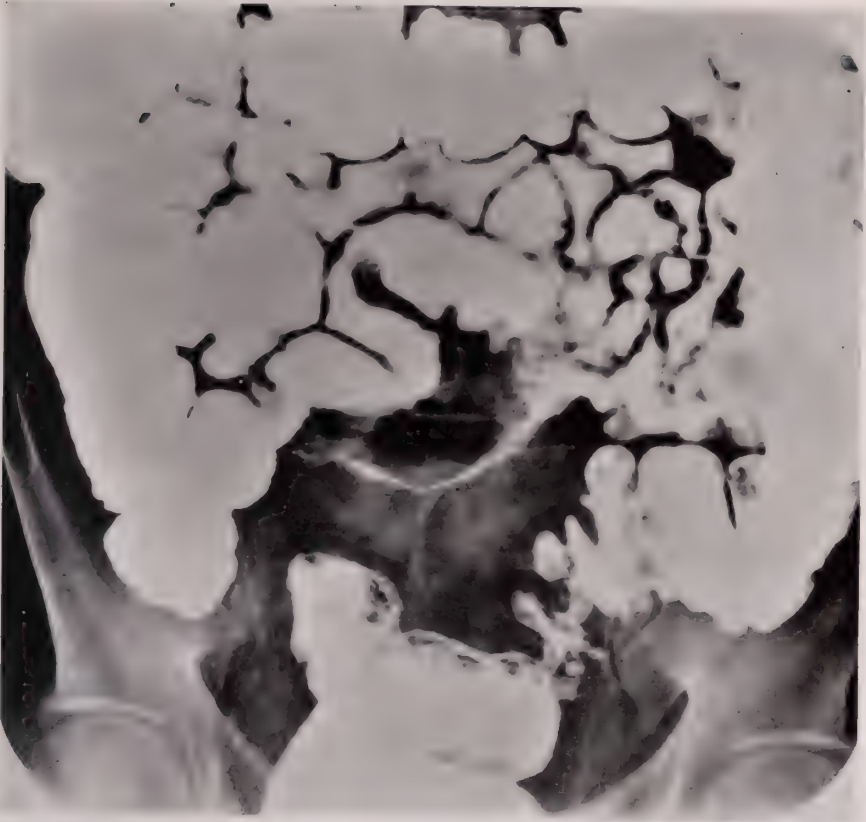


FIG. 2. On a small intestinal series, involvement of the terminal ileum by regional enteritis is seen. The involved loop is separated from adjacent loops by its thickened wall and mesentery. Note the proximity to the sigmoid. No fistulas are seen.

The changes in the sigmoid were undoubtedly due to a perisigmoiditis occasioned by the inflammatory changes in the ileum and mesentery. Regional enteritis producing fistulous communication between the involved ileum and the sigmoid is not uncommon. It is possible that the situation described in this report represents a precursor of this condition.

Obscure roentgen alterations in the sigmoid may be caused by primary lesions in the small intestine. A small intestinal series, in these instances, will aid in establishing the diagnosis.

Final diagnosis: Perisigmoiditis as the presenting feature in terminal ileitis.

CASE NO. 21

A 50-year old male complained of lower abdominal pain without other remarkable symptoms or physical findings. Stools were guaiac negative. Barium enema examination was done and did not appear unusual. Ten months later, the patient complained of rectal bleeding and barium enema was repeated. On spot films (Fig. 1) taken during careful fluoroscopy, a small typical carcinoma was



FIG. 1. Spot film taken during course of barium enema shows a short, rigid, irregular constriction with destroyed mucosal pattern and a distinct overhanging edge distally.



FIG. 2a. Left anterior oblique view of the filled colon shows an "absent haustra" (arrow) or a short, flattened area on the anterior and medial aspect of the proximal sigmoid.



FIG. 2b. Post-evacuation film for mucosal pattern shows an eccentric absence of folds (arrow) over a short distance on the medial aspect of the proximal sigmoid.



FIG. 2c. Double contrast film shows uniform distention of the descending colon and sigmoid, but—there is an arcuate contour convexity towards the lumen (arrow) in addition to the normally distensible contour, convexity directed outwards.



FIG. 2d. Enlarged view of the area indicated by the arrow in Fig. 2c. Flat homogeneous sessile or scalloped defect with smooth surface convex towards the lumen.

found in the proximal sigmoid. On the routine 14 x 17 films of the entire colon including oblique views, this lesion could not be seen. On careful review of the first barium enema examination done ten months previously, very minimal findings could be recognized which even in retrospect are questionable. They may however represent the earliest findings in a carcinoma which starts as a minute sessile filling defect (Fig. 2).

Final diagnosis: Earliest findings in carcinoma of the sigmoid.



FIG. 1. Barium enema examination shows a markedly narrowed segment about 3 cm. in length in the mid-descending colon. The colon proximal to the stricture shows moderate distention and retention of fecal material. The entire colon shows changes indicative of chronic ulcerative colitis. The strictured segment is sharply demarcated proximally, somewhat funnel-shaped distally, and shows no distinct overhanging edges.

CASE NO. 22

A 60 year old female was admitted with a history of recurrent bloody diarrhea for nineteen years diagnosed as non-specific ulcerative colitis. Family history was not contributory. One year prior to the current admission, the patient had been admitted because of persistent vomiting and abdominal distention. A left lower quadrant mass was palpable at that time and barium enema examination (Fig. 1) showed a short, markedly narrowed segment in the mid-descending colon. Operative intervention was contemplated but postponed because of a transfusion hepatitis. All symptoms improved considerably on simple therapy and patient was discharged. The current admission was required because of recurrent vomiting and distention, fever, leucocytosis, and tenderness in the left lower



FIG. 2. The examination one year later shows very irregular filling at the strictured site with small nodular defects and multiple sinus tracks.

quadrant. Repeat barium enema examination (Fig. 2) showed marked narrowing and irregularity with incomplete obstruction and multiple sinus tracks at the site of the previous stricture in the descending colon.

Subtotal colectomy was performed. The lesion in the descending colon was markedly indurated with diffuse thickening of the bowel wall. Grossly, differentiation between an inflammatory and neoplastic process could not be made. Microscopically, there was an extensive infiltrating carcinoma with predominantly intramural growth.

Final diagnosis: Scirrhus carcinoma of the colon in long-standing ulcerative colitis presenting as a stricture with sinus track formation.

CASE NO. 23

A 55 year old male was admitted with a history of episodes of bloody diarrhea attributed to ulcerative colitis at long intervals over a period of 29 years. Family history was not contributory. The last severe episode had occurred fifteen years prior to admission. For eight years, patient had been kept on small maintenance doses of steroids. Over a period of six months, patient complained of occasional abdominal cramps relieved by insertion of a rectal tube. A marked stricture just within the anal canal required periodic dilatation. Biopsy of the stricture was negative for carcinoma. One week prior to admission, abdominal cramps became more severe, associated with abdominal distention, severe constipation and tenesmus. Physical examination showed a well-nourished, husky



FIG. 1a. Barium enema examination shows a markedly narrowed segment 2 to 3 cm. in length in the mid-descending colon with moderate dilatation of the colon proximal to it. The irregular contours of the colon and the loss of haustral and mucosal pattern indicate a chronic ulcerative colitis which does not appear to be remarkably active at this time.



FIG. 1b. Same examination. The stricture in the descending colon shows no distinct overhanging edges. The medial aspect of the dilated colon immediately proximal to the stricture shows constant flattening and suggestive rigidity.

male with abdominal distention. Hemoglobin was 14.8 gms per cent. An annular stricture three inches from the anus was dilated and a rectal tube was inserted with passage of gas and considerable relief to the patient. However, barium enema examination (Figs. 1a, 1b) showed a strictured segment 2 to 3 cm. in length in the mid-descending colon and changes throughout the colon indicative of chronic ulcerative colitis. Differentiation between a benign and a malignant stricture could not be made with certainty.

Because of the excellent condition of the patient and the absence of symptoms attributable to activity of the ulcerative process, it was tempting not to operate upon this patient in an effort to avoid total colectomy. Nevertheless, because the possibility of carcinoma could not be excluded, exploration was performed and a stricture 2 cm. in length and 5 mm. in diameter with markedly thickened bowel wall and serosa was found. Because the adjacent bowel did not appear actively inflamed, only a local resection was performed. The gross appearance of the specimen suggested a chronic inflammatory process, particularly since a sinus track was found extending into the serosal fat. The mucosa at the proximal margin of the stricture showed several flat, shallow, irregular ulcerations and a somewhat nodular slightly raised surface. Three polyps on long pedicles were found at some distance from the stricture. Microscopic examination showed a stenosing infiltrating mucoid adenocarcinoma with pericolic abscess. One involved lymph node was present. Changes of old chronic, non-specific ulcerative colitis with inflammatory polyps were also noted.

Final diagnosis: Scirrhus carcinoma of the colon in a long-standing ulcerative colitis presenting as a stricture.

CASE NO. 24

Submitted by
JOHN E. MOSELEY, M.D.

A 38 year old colored cook was admitted with the chief complaint of pain in both hips and in the left shoulder of four years duration. Physical examination

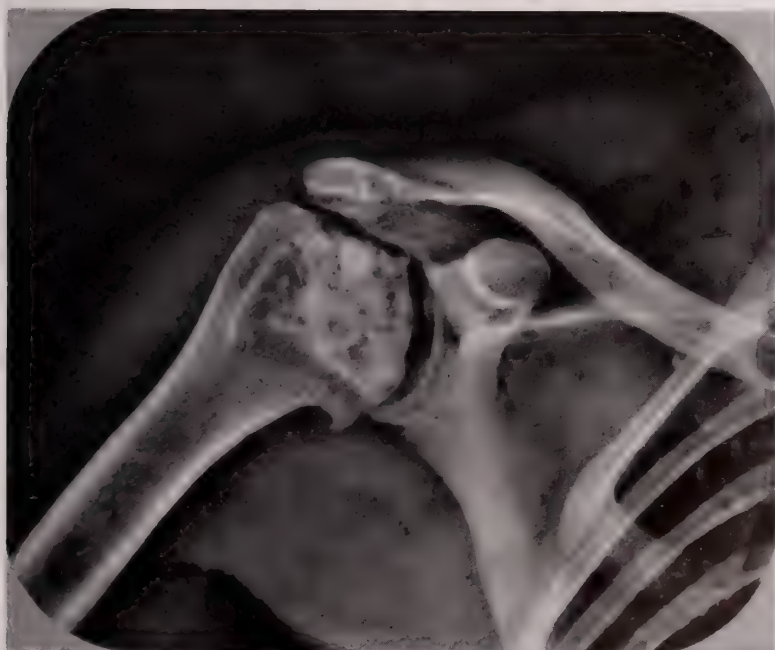


FIG. 1. Left shoulder shows diffuse, somewhat mottled, sclerosis of the head of the humerus with marked flattening and irregularity of the articular cortex.

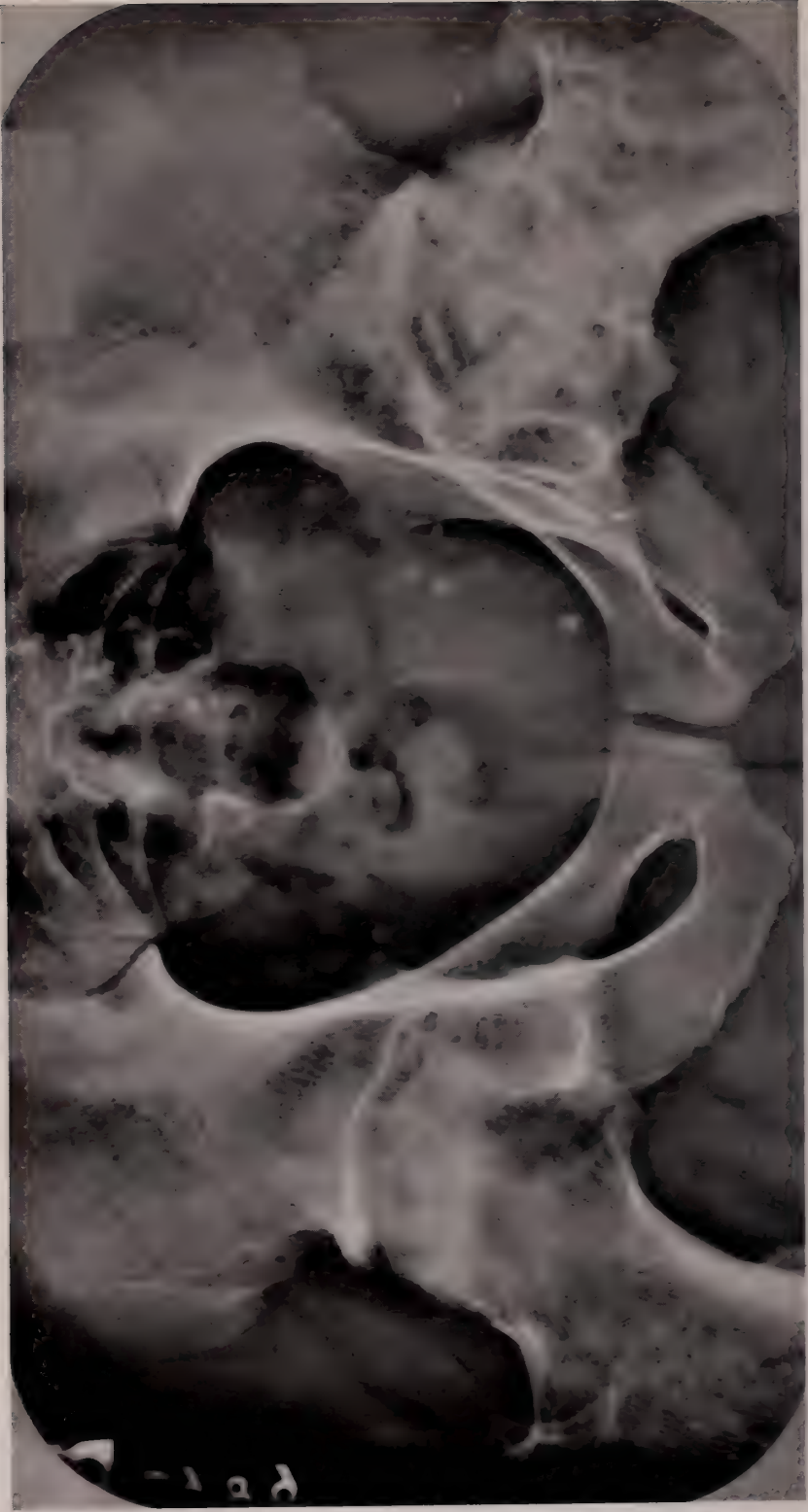


FIG. 2. Marked sclerotic changes with irregularities and rarefaction in both femoral heads with moderate flattening. Secondary hypertrophic arthritic changes on both sides, more marked on the left.

revealed marked limitation of abduction and rotation of the left shoulder and marked limitation of motion in all directions of both hips. There was no history of trauma or of any occupation other than cooking. Laboratory findings showed a hemoglobin of 14 gms per cent; R.C.B., 4,650,000 per cu. mm.; W.B.C., 5900 per cu. mm. with 57 per cent neutrophils, 40 per cent lymphocytes, 3 per cent monocytes. Calcium and phosphorus were normal, alkaline phosphatase was 3.8 Bodansky units. The Kline and Mazzini tests were negative. Urine analysis was not remarkable. Serum bilirubin was 0.3 mg. per cent (direct). X-ray examination of the chest showed no evidence of cardiac enlargement; lungs were not remarkable. X-ray examination of the left shoulder (Fig. 1) showed diffuse sclerosis with areas of bone resorption in the head of the humerus. X-ray examination of the right shoulder showed very similar findings. Examination of the hips (Fig. 2) showed extensive sclerotic changes with irregular areas of rarefaction in the heads of both femora.

The changes in the shoulders and hips suggested the diagnosis of sickle-cell anemia. However, despite the fact that 100 per cent sickling was present after 24 hours, the patient was not anemic and the clinical course was too benign for this diagnosis in a patient of his age. Electrophoretic studies revealed sickle-cell and C hemoglobins. Bone changes in the shoulders and hips such as seen in this case appear to be particularly common with this combination of abnormal hemoglobins. The correct diagnosis may be suggested from the association of such changes with a benign clinical course.

Final diagnosis: Sickle cell—hemoglobin C disease.

CASE NO. 25

A 24 year old ex-Marine was admitted because of the finding on a routine chest film of a "mediastinal tumor". The patient had no specific complaints, no limitation of activity nor any dyspnea on exertion. In fact, two years prior to admission, he had completed six weeks of basic training in the Marine Corps without difficulty. However, he had always been slight in stature and underweight.

Physical examination showed a slight male who appeared younger than his stated age. The heart was enlarged with an occasional premature contraction. In the apical region, there was a grade II harsh systolic murmur and a mid-diastolic murmur with a presystolic crescendo. There was a loud harsh systolic murmur in the left 2nd intercostal space audible also in the back. P2 was louder than A2 and was split. Blood pressure was 120/80, pulse was 100 and respiratory rate was normal. There was no evidence of cyanosis, clubbing or peripheral edema. The liver and spleen were not palpable. Hemoglobin was 14.5 grams per cent; red blood count, 4.5 million per cu. mm. with a hematocrit of 50 per cent. Electrocardiogram showed right axis deviation with wide notched T waves and high voltage of the P waves and QRS complexes. The resting oxygen saturation of the peripheral blood was 92 per cent. After a standard exercise test, the oxygen saturation showed a somewhat abnormally large decrease to 87 per cent. The decholin circulation time was 7 seconds. The ether circulation time was 4 seconds with almost immediate facial paresthesias.

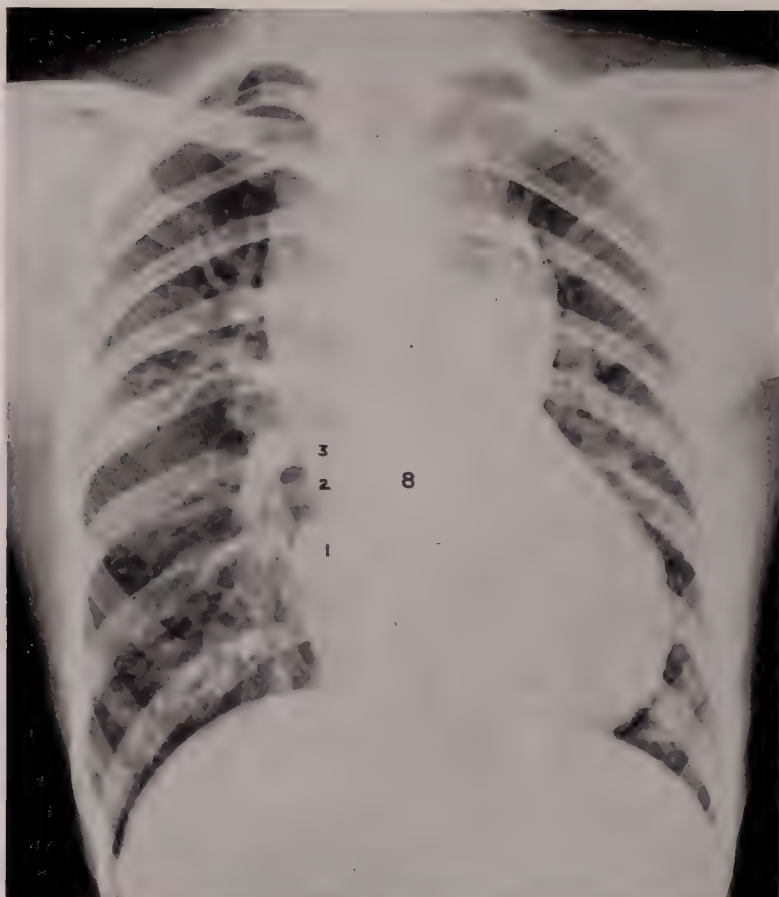


FIG. 1. Postero-anterior projection of the chest shows marked widening of the superior mediastinum both to the right and to the left. The aortic knob of normal size can be seen faintly through the shadow of the widened superior mediastinum. In addition, through this shadow, large vascular markings are seen extending into both upper lobes. The transverse diameter of the heart is increased and the left cardiac contour somewhat globular in configuration. The region of the main pulmonic artery segment is straightened but there is no evidence of marked bulging. The left hilum is obscured. The right hilar vessels are not unusually large but pulsated vigorously on fluoroscopy. In addition, several large segmental veins from the medial portion of the base of the right lung run upwards and medially to fuse into a large band-like density which can be faintly seen through the right side of the heart. This shadow is lost in the shadow of the spine at the level of the 8th dorsal vertebra. The band-like density through the shadow of the heart is indicated by the numeral 1 and the number 8 indicates the level of the 8th dorsal vertebra. In addition numbers 2 and 3 indicate a confluence of veins in the region of the lower part of the right hilum which extend horizontally into the mediastinum at the level of the 8th dorsal vertebra.

Roentgen examination of the chest (Fig. 1) showed marked widening of the superior mediastinum both to the right and to the left with laterally bulging convex contours. A normal sized aortic knob could be seen through the shadow of the widened mediastinum. In addition, through this shadow, on both sides of the spine, could be seen numerous large vascular markings extending into both upper lobes. The transverse diameter of the heart was increased and the left



FIG. 2. Left anterior oblique projection of the chest with barium in the esophagus demonstrates a long, relatively shallow, constant indentation on the anterior wall of the esophagus centered at the level of the 8th dorsal vertebra. In addition, through the shadow of the heart, the large segmental veins from the base of the right lung can be seen to fuse into a broad band-like shadow (arrow) which ascends to the region of the esophageal indentation.

cardiac contour somewhat globular in configuration. The region of the main pulmonary artery segment appeared to be straightened but there was no remarkable bulging in this area. The left hilum was obscured in the postero-anterior projection. The vessels at the right hilum did not appear to be unusually large but on fluoroscopic observations showed very active pulsations. In addition, several rather large vascular markings in the medial portion of the base of the right lung appeared to fuse into a single broad trunk which could be faintly seen within the shadow of the right side of the heart to extend upwards and medially to be lost in the shadow of the vertebral column. Just above this vessel, there was a confluence of several large veins which extended horizontally also to be lost in the

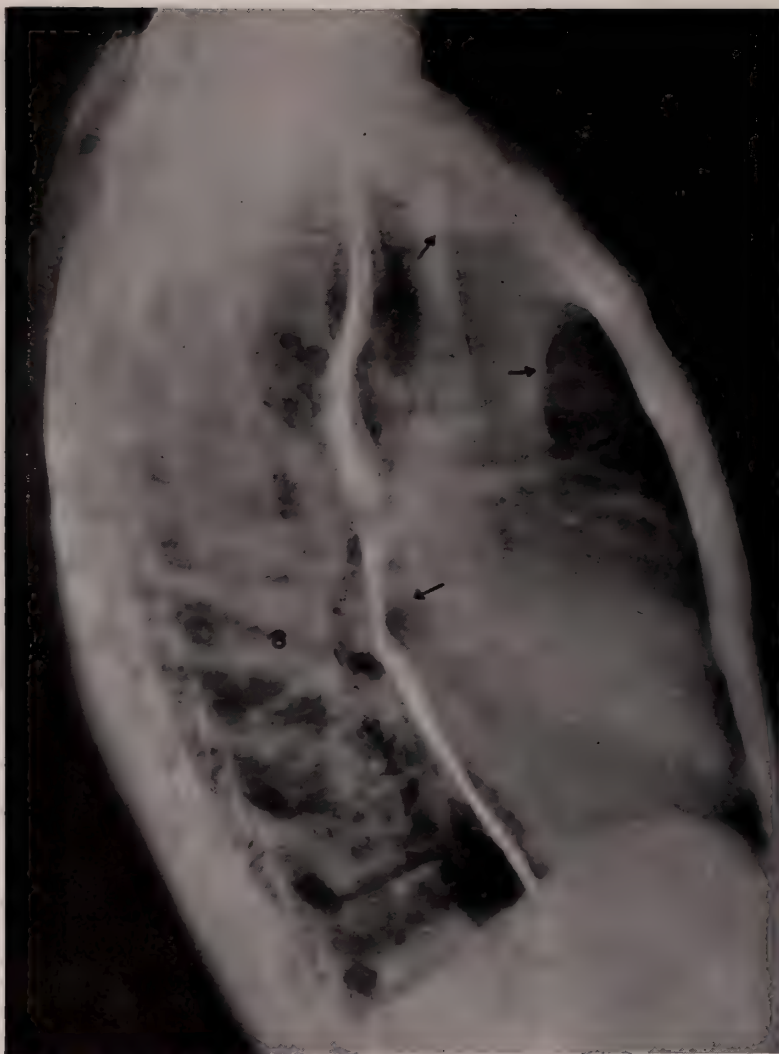


FIG. 3. Lateral view of the chest with barium in the esophagus shows a rather long but normally situated aortic indentation. In addition (lowermost arrow) there is a second indentation on the anterior aspect of the esophagus below the level of the tracheal bifurcation. Anterior to this there is a rather globular homogeneous density which is presumably vascular. Moreover, there is a vertical, homogeneous, quadrilateral density in the anterior mediastinum in front of the trachea, (middle arrow) which is sharply demarcated and concave anteriorly. The uppermost arrow indicates a rather marked prominence of the soft tissues at the thoracic inlet. (The vertical line a short distance in front of the trachea is the soft tissue shadow of the arm which is raised directly upwards.)

shadow of the vertebral column at the level of the 8th dorsal vertebra. Barium swallow (Figs. 2, 3) showed an aortic indentation in its normal location which appeared to be somewhat elongated. In addition, there was a second discrete indentation on the anterior aspect of the esophagus below the tracheal bifurca-

tion at the level of the 8th dorsal vertebra. In the left oblique projection, the large draining vein of the right lower lobe could also be seen through the cardiac shadow to extend upwards to the region of the indentation on the esophagus.

The postero-anterior projection in this patient has an appearance of the heart and mediastinum which has been referred to as a "figure-of-8" configuration,—the widened superior mediastinum representing the upper loop and the cardiac shadow the lower loop. This is said to be typical of total anomalous pulmonary venous drainage, that is, a condition in which the pulmonary veins from the right lung join the pulmonary veins from the left lung to the left of the midline and then enter an anomalous persistent vertical vein or left superior vena cava which drains into the left innominate vein and finally into the normal right superior vena cava and back to the right side of the heart. In this condition, there must be an associated intracardiac defect, specifically an interatrial defect, to permit oxygenated blood to enter the systemic circulation. The diagnosis of anomalous pulmonary venous drainage was suggested from the roentgen examination, not only because of this configuration, but because of the evidence of the large anomalous draining veins from the right lower lobe crossing in front of the esophagus to the left side of the mediastinum. This diagnosis was confirmed by catheterization and angiocardiographic studies. These studies were not sufficiently extensive to prove that *total* anomalous drainage was present. This appears unlikely since this patient has had a relatively benign clinical course and does not show cyanosis. The roentgen findings indicate that there is anomalous drainage at least from the right lower lobe and probably also from the right middle lobe and it is assumed that there is at least partial anomalous drainage also from the left lung and an intracardiac compensatory defect.

Final diagnosis: Anomalous pulmonary venous drainage; extrinsic pressure on the esophagus by anomalous pulmonary venous trunk.

CASE No. 18 TRICHOBEZOAR WITH ENMESHED METALLIC FOREIGN BODIES

CASE No. 19 INTRACRANIAL POSTERIOR FOSSA DERMOID CYST

CASE No. 20 PERISIGMOIDITIS AS THE PRESENTING FEATURE IN TERMINAL ILEITIS

CASE No. 21 EARLIEST FINDINGS IN CARCINOMA OF THE SIGMOID

CASE No. 22 SCIRRHOUS CARCINOMA OF THE COLON IN LONG-STANDING ULCERATIVE COLITIS PRESENTING AS A STRICTURE WITH SINUS TRACK FORMATION

CASE No. 23 SCIRRHOUS CARCINOMA OF THE COLON IN LONG-STANDING ULCERATIVE COLITIS PRESENTING AS A STRICTURE

CASE No. 24 SICKLE CELL—HEMOGLOBIN C DISEASE

CASE No. 25 ANOMALOUS PULMONARY VENOUS DRAINAGE; EXTRINSIC PRESSURE ON THE ESOPHAGUS BY ANOMALOUS VENOUS TRUNK

THE USE OF A PRONE PRESSURE DEVICE IN INTRAVENOUS
CHOLANGIOGRAPHY

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AND

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The detection of abnormalities in the extrahepatic biliary system in the cholecystectomized patient has been a thorny problem. With the introduction of intravenous cholangiography, it has been possible to find sufficient anatomical and physiological evidences to diagnose or preclude the presence of disease. The procedure is now a routine one and many technics for its satisfactory performance have been suggested.

A common difficulty encountered technically is the presence of intestinal shadows superimposed upon the lumen of the opacified common and major hepatic ducts which may simulate or even obscure intraluminal filling defects. In many cases, adequate cleansing of the colon is not always possible or accomplished. Frequently, despite proper preparation of the colon, small intestinal shadows still overlap the area of interest.

Sectional radiography has been utilized to free the common and major hepatic ducts from the interference of overlying gas shadows. This procedure has been extremely helpful; however, it is lengthy and not always available. Furthermore, the patient may receive more radiation with this method than he would with conventional filming.

In view of these factors, a pressure device to displace troublesome gas shadows has been utilized with conventional filming. This device has enabled us to achieve, in almost all cases in which the biliary tract is visualized, satisfactory demonstration of the extrahepatic biliary tree.

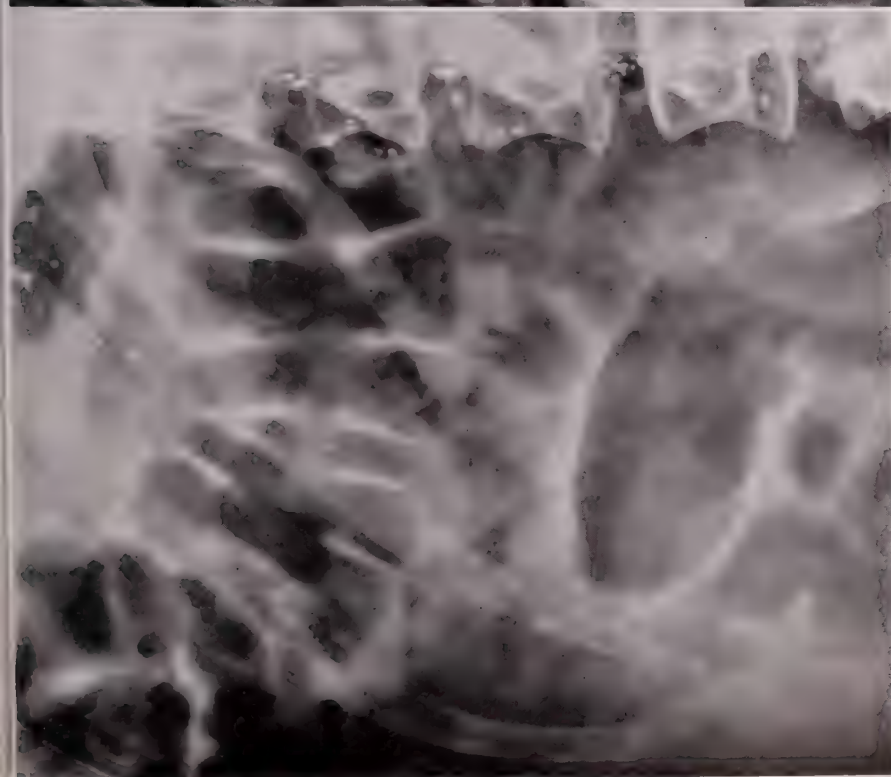


Fig. 1A

Fig. 1A. Twenty minutes after the intravenous injection of Cholangiogram. The extrahepatic biliary tract is not visualized. Details of the right upper quadrant are largely obscured by intestinal gas shadows.



Fig. 1B

Fig. 1B. Same patient as Figure 1A. The patient was placed upon the prone pressure device after preceding film was seen. The intestinal shadows have been displaced caudally and the common duct is clearly visible now.



FIG. 2A

FIG. 2A. Thirty minutes after the injection of Cholografin. The common and major hepatic ducts are well opacified. The distal third of the common duct is partially obscured by overlying intestinal shadows and a stone cannot be excluded.

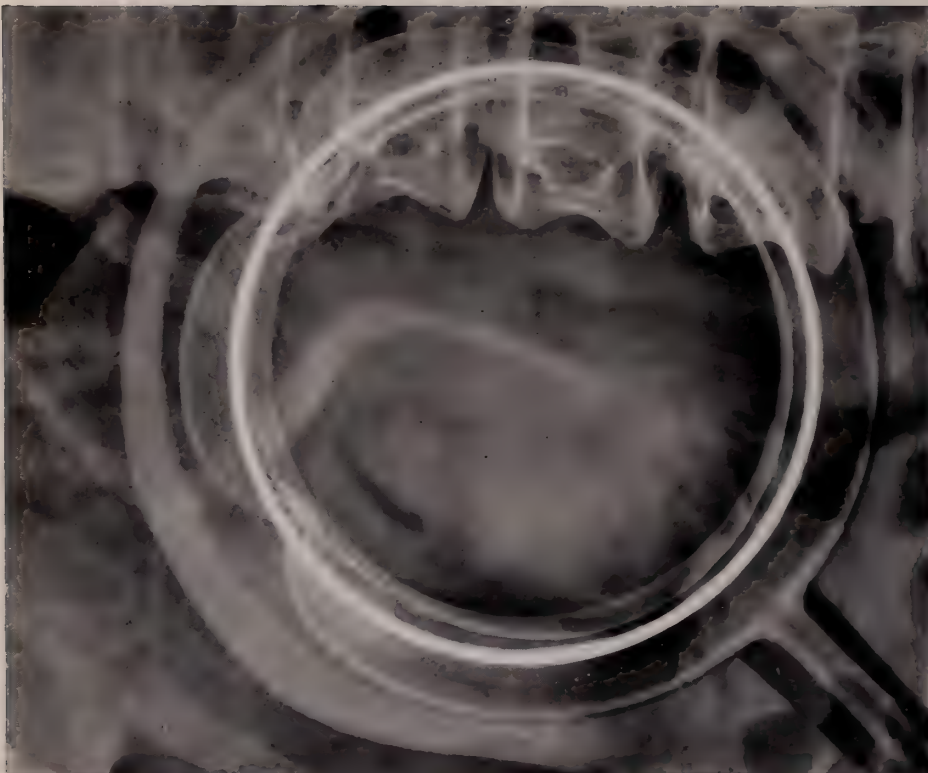


FIG. 2B

FIG. 2B. Shortly thereafter, the patient was placed on a prone pressure device. The lower end of the common duct and the presence of the opaque stone are well opacified.



Fig. 3A

Fig. 3A. Thirty minutes after the intravenous injection of Cholegrafin. The shadow of the common duct appears hazy and intestinal shadows overlie the lower third.



Fig. 3B

Fig. 3B. On the prone pressure device, the common and major hepatic ducts are now clearly seen. The intestinal shadows have been displaced. Note the presence of a cystic duct stump which could not be seen on the preceding film.

DR. RALPH COLP AWARD

The prize committee, consisting of the chairmen of the Committee on Medical Education, the Director of Surgery, and the editor of the Journal of The Mount Sinai Hospital has met. It has unanimously chosen the paper by Edward Bergofsky, entitled, "The Prognosis in Patients with Esophageal Varices Discovered Prior to Bleeding", which appeared in Volume 23, page 263, of the Journal of The Mount Sinai Hospital, for its first award.

In the judgment of the committee, this paper showed original thinking and threw light on the as yet unsolved question of whether esophageal varices which have not bled should be operated upon.

Under the terms of the award, the money earned by the Dr. Ralph Fund established by his colleagues and friends, is to be awarded to "the best paper by a member of The Mount Sinai Hospital house staff published in the Journal of The Mount Sinai Hospital, preference to be given to a surgical subject".

DUCTULAR CELL REACTION IN THE LIVER IN HEPATIC INJURY

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Rats which are exposed to various agents injurious to the liver exhibit, besides damage of the hepatic cells, an accumulation of cells between the liver cell plates and the wall of the sinusoids which fail to display, at least on superficial inspection, any organization. These interstitial cells occur in a variety of intoxications and are especially prominent in ethionine, thioacetamide, senechio, dimethylnitrosamine and butter yellow intoxications. These interstitial cells have been pointed out by Gillman et al and also demonstrated in biliary obstruction (1). Farber (2) described these cells as oval cells, discussed their relation to hyperplasia and suggested their origin from bile duct epithelium, as did Lopez (3) in the case of thioacetamide intoxication. In a study of the histogenesis of experimental cirrhosis and its relation to cancer, an investigation of this interstitial cell reaction became pertinent with special emphasis on its morphology, its origin, its effects, its relation to liver damage, to inflammation and to neoplasia as well as its presence in other species, especially the human.

Interstitial cells appear in subacute intoxications sometimes associated with damage to the hepatic cells, as for instance after several weeks of a diet containing 0.3 Gm. ethionine per 100 Gm., in clusters (Fig. 1) intermixed with unquestionable inflammatory cells such as lymphocytes and segmented leukocytes. They exhibit at this time round nuclei with hardly visible nucleolus. They clearly differ from the Kupffer cells since, in contrast to the latter, the interstitial cells fail to show phagocytosis, especially after intravascular injection of ink during life (Fig. 2). When the process progresses further, for instance because of the continuation of the diet, the inflammatory cells disappear, the nuclei of the remaining interstitial cells become elongated and the cells arrange themselves in single or double file (Fig. 3). This becomes especially apparent during recovery when the liver cells have become entirely normal while the interstitial cells may persist and may resemble fibroblasts.

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Presented before the American Society for Experimental Pathology (Federation of American Societies for Experimental Biology) in Chicago on April 18, 1957.

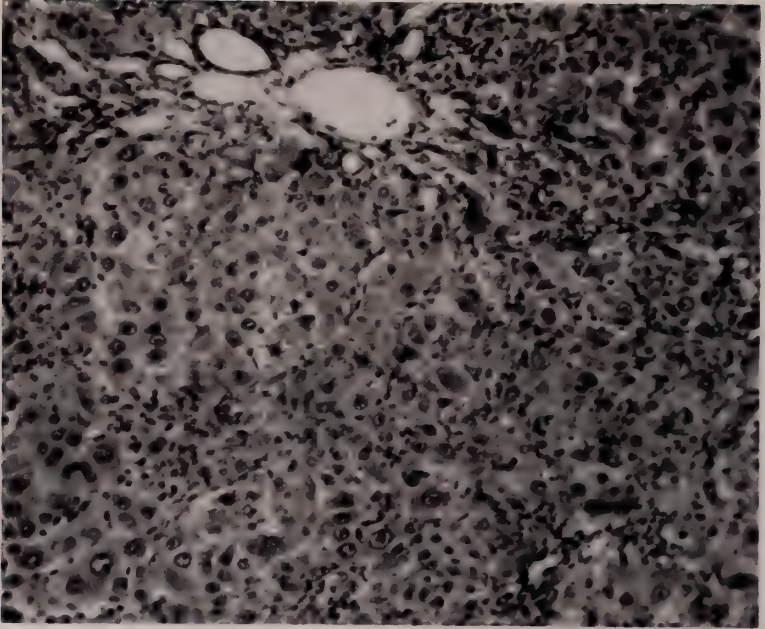


FIG. 1. Liver of rat which had been for 42 days on a diet containing 0.5% ethionine. Clusters and strands composed of interstitial cells, most of which are ductular cells and few of which are lymphocytes and segmented leukocytes, are noted between the liver cells. The latter show diffuse degeneration with single cell necrosis and degeneration. H & E. (130X)

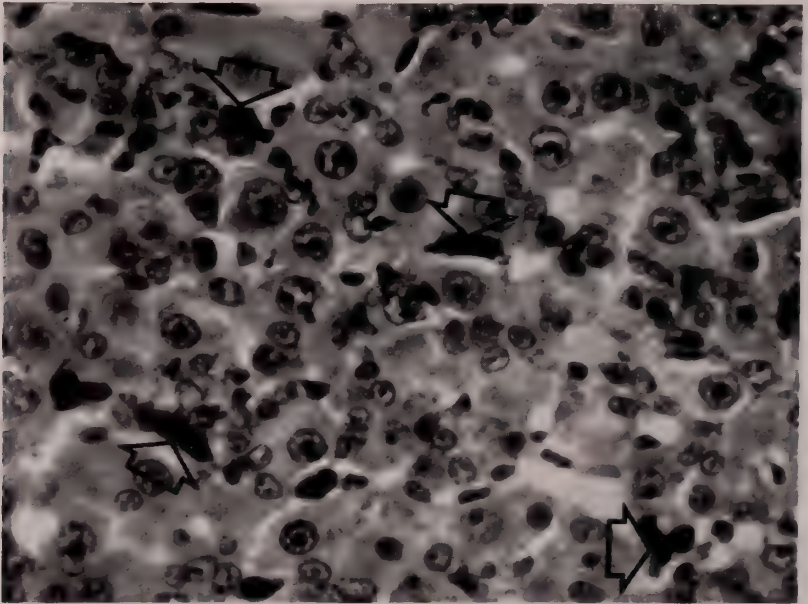


FIG. 2. Liver of rat which had been for 40 days on an 0.5% ethionine containing diet and which had received India ink intravenously shortly before sacrificing. Severe interstitial cell reaction (composed of ductular and inflammatory cells).

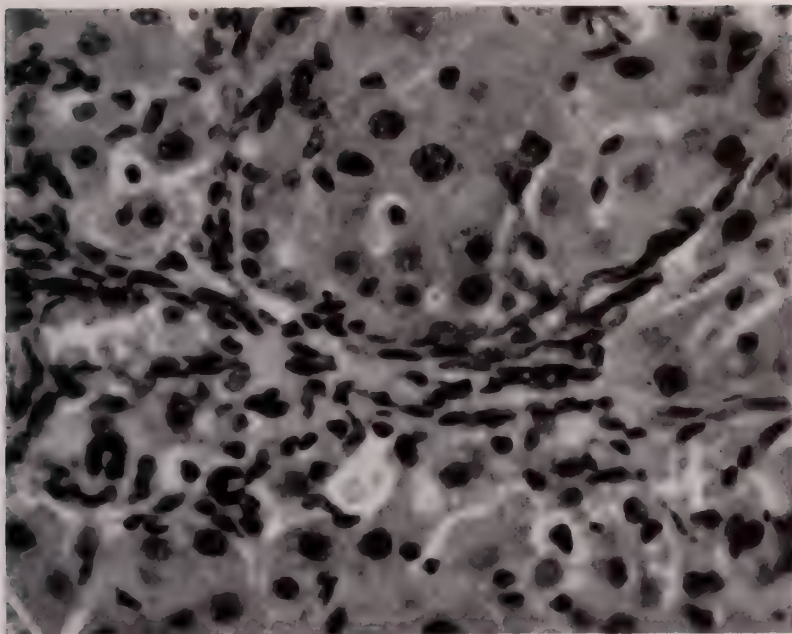


FIG. 3. Liver of rat which had been for 68 days on an 0.5% ethionine containing diet. Most of the interstitial cells have spindle shape and some resemble fibroblasts. H & E. (450X).

In the cytoplasm of the interstitial cells, phosphatase can be demonstrated histochemically in contrast to the hepatic cells and in analogy to bile duct and ductular epithelium. The bile ductular nature of the majority of the interstitial cells is also suggested by the occasional appearance of lumina but is clearly proven if India ink is injected, at the time of sacrificing, into the bile duct. Under such circumstances, fine canaliculi with characteristic ramifications are ink injected within clusters of otherwise mesenchymal appearing cells. Moreover, in one micron thick sections, fine cuticular membranes can be demonstrated in disorganized appearing ductular cells. This membrane can be impregnated with silver (Fig. 4).

In earlier stages, the ductular cells, organized or disorganized appearing, are predominantly found on the lobular periphery and seem to derive by sprouting from preformed ductules and ducts and exhibit many mitoses. In later, especially florid, stages, the impression is sometimes gained of a transition between ductular cells and neighboring hepatic cells without mitoses. This is particularly suggestive in thin sections and would suggest a transformation of liver cells into ductular cells as is now known to occur in embryonal life (4).

Ductular cell proliferation seems to interfere with blood circulation. In the normal rat, following supravital injection of ink into the portal vein, the carbon is uniformly distributed in the sinusoids around the portal tract but does not reach the central vein. In contrast, in ethionine intoxication, ink is only found in few irregularly scattered sinusoids and appears immediately in the central vein. This indicates a shunt interfering with normal blood supply to the paren-

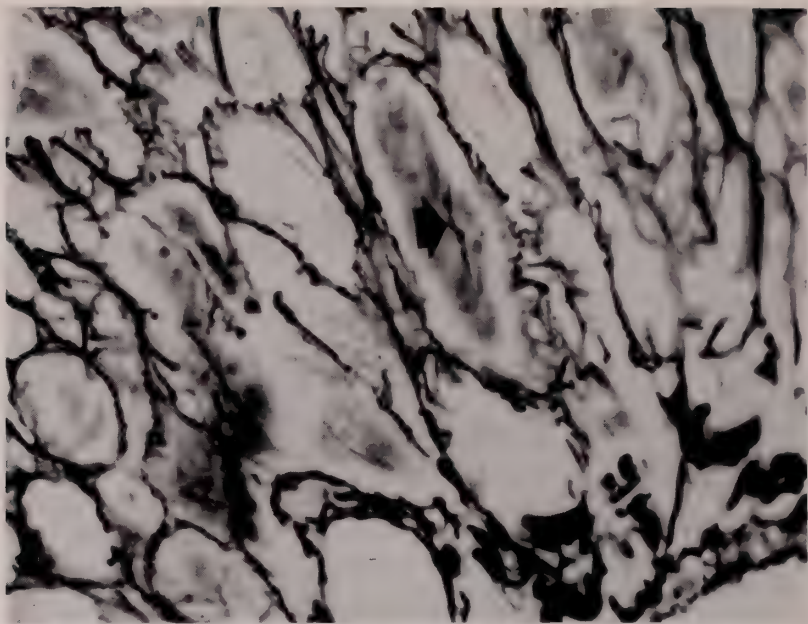


FIG. 4. Basement membrane formation around organized and disorganized ductular cells and silver impregnation (arrow) of cuticular lining of ductular cells. Gomori silver impregnation. (610X).

chyma. Nevertheless, even if the ductular cell proliferation should contribute to the damage of the hepatic cells, it is not its only cause because, upon administration of cortisone to ethionine intoxicated rats, the interstitial reaction, including both accumulation of inflammatory cells as well as proliferation of ductular cells, is almost entirely inhibited while the hepatocellular damage persists.

Ductular cell proliferation is usually associated with conspicuous increase in argentaffine fibers which arrange themselves as basement membranes around the organized and not obviously organized ductular cells (Fig. 4). Later these cells, sometimes morphologically resembling fibroblasts, are surrounded by argentaffine membranes. The latter become subsequently approximated after collapse of the parenchyma. They give eventually collagen reaction and are transformed into connective tissue septa which may subdivide the lobule to nodules and thus initiate cirrhosis formation (5). In this sense the ductular cell proliferation may provide a stimulus for fiber formation, this specific role requiring further investigation.

The inhibition of the interstitial and especially ductular cell reaction by cortisone suggests a resemblance of this reaction to an inflammatory process. Relation to neoplasia is suggested by its appearance after carcinogenic drugs. Moreover, in the neighborhood of liver cell breakdown products, even disorganized appearing ductular cells may rearrange themselves in the form of well organized ducts. Particularly in some aspects of the circumference, the epithelial cells

become high columnar and their cytoplasm markedly basophilic. This is associated with accumulation of inflammatory cells and excessive circular fibrosis and thus presents the initial stage of cholangiofibrosis as pointed out by Farber. The relation of this reaction to neoplasia requires further investigation. However, it deserves emphasis that disorganized groups of ductular cells may invade vessels, in the lumen of which they reassume the shape of liver cells.

These observations raise the question as to whether similar features may occur in other conditions and especially in other species than the rat. They develop after bile duct ligation with superimposed infection when the excessive bile duct proliferation becomes disorganized (Fig. 5). They may be seen in guinea pigs around tuberculous granulomas when the ductular proliferations may become disorganized, similarly associated with fibrosis, and especially when the impression is gained that these ductular cells appear to contribute to the epithelioid cells of the granuloma itself.

In the human, accumulation of disorganized appearing ductular cells often surrounded by inflammatory cells may be found within the lobular parenchyma and may then be mistaken for focal necrosis or may account for so-called inflammation in the portal tract, both features being seen particularly in non-specific injuries (reactive hepatitis). Accumulations of organized and disorganized appearing ductular cells are also conspicuous in cirrhosis, particularly in florid phases, and on the border between lobular or nodular parenchyma and the septa. They are clearly associated with fibrosis.

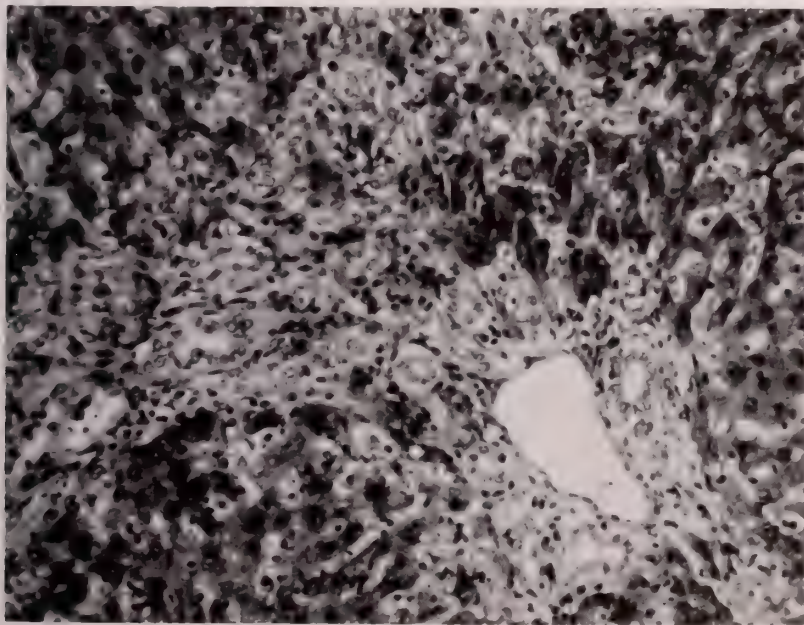


Fig. 5. Liver of rat 14 days after ligation of the bile duct and subsequent *E. coli* infection. Marked increase of organized and disorganized ductular cells on the lobular periphery intermixed with segmented leukocytes and separating the liver cells. H & E. (150X).

SUMMARY

In conclusion, the interstitial cell reaction appears to be a response of the liver to injury. It consists sometimes of inflammatory cells but mainly of organized and disorganized appearing ductular cells, derived from bile ducts or ductules but possibly also from liver cell plates. The reaction interferes with sinusoidal blood flow but liver cell damage present may be independent of it. It stimulates fibrosis over basement membrane formation. Its relation to inflammation and neoplasia is still conjectural. Though most conspicuous in the rat, it occurs in other species, including the human. The ductular cells seem to contribute to granuloma formation. However, their relation to mesenchymal cells, which they resemble and with which they are frequently associated, cannot yet be decided.

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A METHOD OF ANALYZING ELECTROCARDIAC ENTITIES IN SPACE*

II: SPHERICAL VECTORCARDIOGRAPHY: THE USE OF A SPHERE TO DETERMINE ANGLES, PLANES, ROTATION, VELOCITY AND TORTUOSITY

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The heart has often been pictured as lying at the center of an imaginary sphere (1-7). For our purpose, an abstract point source of dipole current, or its graphic representation, the null-point, is centered within an actual sphere. The representation of vectorial axes as points on the surface of this sphere (8) initiates the complete spatial analysis of the cardiac cycle.

All vectors take origin at a single point and as their axes diverge subtend angles and planes. It is intended here to advance a simple method of determining these angles and planes and to propose certain terms and criteria by which they may be completely described and fixed in space.

The sphere is ideally suited to this purpose. The arc distance between two points on its surface is proportional to the angle subtended by radii to these points. It is therefore termed the angular distance and expressed in degrees. If the null-point be considered as lying at the center of a sphere, two divergent vectors will pierce its surface at distinct points. If we can indicate the position of these points on a material sphere, the arc distance between them will be a measure of the angle subtended by the vectors. The fact that the arc itself lies on the plane of the vectors will be utilized to determine this plane.

In the exposition that follows these expressions and principles will be borrowed from the fields of navigation, mine surveying, and spherical trigonometry that are most suitable or descriptive. Although such terms as latitude, longitude, East and West are alien to the lexicon of the electrocardiographer, their familiarity is a convenient aid to the visualization and understanding of the method.

If a plane be passed through a sphere, the line of intersection is a circle. The largest possible circle is one whose radius is equal to that of the sphere. This is a great circle; its plane cuts the centre of the sphere. There are an infinite number of such circles. Those which pass through the poles are called meridians, and the angular distance between each meridian and a pre-chosen, or prime meridian, is expressed as an angle of longitude. The equator of a sphere is also a great circle. It is perpendicular to the meridians and may be considered as lying on the horizontal plane. The planes of the meridians are then horizontal projecting planes. A plane that passes through a sphere, but not through its centre, cuts

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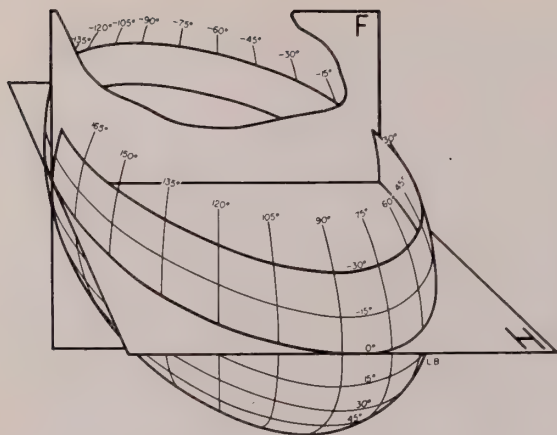


FIG. 1a



FIG. 1b

FIG. 1a. The sphere. Longitude is measured from the left half of the frontal plane and ranges from 0° to $\pm 180^\circ$. The anterior hemisphere is positive; the posterior negative. Latitude ranges from 0° to $\pm 90^\circ$. The lower hemisphere is positive; the upper, negative.

FIG. 1b. Markings for angular distance on moveable meridian.

off a small circle; its radius is less than that of the sphere. Small circles parallel to the equator are called parallels, or circles, of latitude. The latitude of a point is its angular distance from the plane of the equator. Longitude is measured from the left half of the frontal plane and ranges from 0° to $\pm 180^\circ$. The anterior hemisphere is positive; the posterior, negative. Latitude ranges from 0° to $\pm 90^\circ$, the lower hemisphere is positive; the upper, negative. The graticulations are so annotated in fig. 1a. The reader may have surmised that the spherical coordinates azimuth and elevation, may be supplanted by those of geography of astronomy, longitude and latitude, respectively.

Vector \overline{OB} is presented orthographically in fig. 2a. Its azimuth is 135° . Its elevation is found by revolution to be -75° . If its origin be centered within a sphere of radius equal to its magnitude, as in fig. 2b, its terminus will touch the surface at the intersection of the -75° parallel of latitude and the 135° meridian of longitude, as in fig. 2c. The axis of \overline{OB} may then be represented by a single point on the surface of the sphere, as in fig. 2d.

Let us return to our hypothetical case of left bundle-branch block (see Part I) (10). The areas of P, QRS, and T were measured algebraically in the XYZ leads by planimetry, and the spherical coordinates of these integrals, annotated as \bar{P} , \overline{QRS} , and \bar{T} , determined. The spatial ventricular gradient, \overline{VG} , was also obtained by adding the areas of QRS and T. The effect of atrial repolarization on the ventricular complex is disregarded here to avoid complexity. The values are listed in Table I.

As an axis may be represented by a point on the surface of a sphere, the axes of \bar{P} , \overline{QRS} , \bar{T} , and \overline{VG} have been so marked on an actual sphere. This is slated and takes chalk or white charcoal. A ping-pong ball or a small terrestrial globe are quite satisfactory. It has two poles, north (N) and south (S), and is graticulated with parallels and meridians.

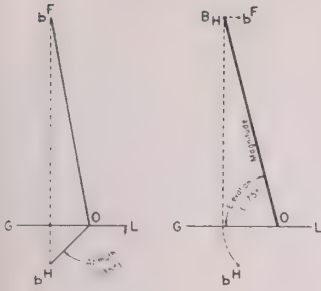


Fig 2a

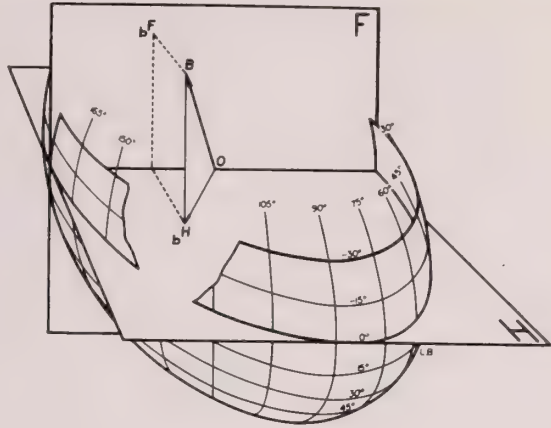


Fig 2b

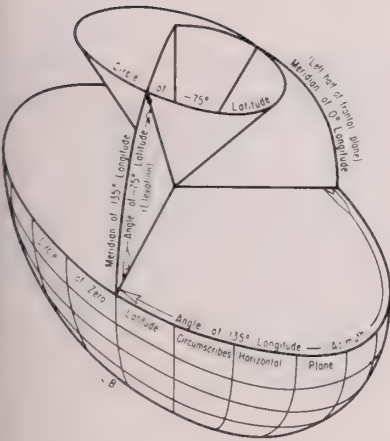


Fig 2c

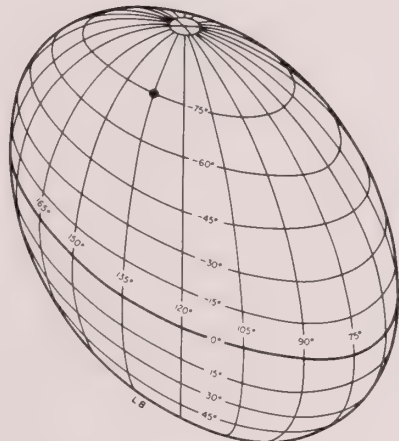


Fig 2d

FIG. 2a. Orthographic representation of vector \overline{OB} . Azimuth (135°) is the angular distance between its horizontal projection and the left half of the ground-line. Magnitude and elevation (-75°) are found by revolution.

FIG. 2b. The origin is centered within a sphere of radius equal to its magnitude.

FIG. 2c. As azimuth is equal to longitude and elevation to latitude, the terminus of \overline{OB} touches the surface of the sphere at the intersection of the 135° meridian of longitude and the -75° parallel of latitude.

FIG. 2d. The axis of \overline{OB} may therefore be represented by a point on the surface of the sphere.

\overline{QRS} , \overline{VG} , and \overline{T} are seen in fig. 3a, a view from the third quadrant (below and behind). Each is shown as a round spot whose radius is proportional to the magnitude of the vector it represents. This is more than an improvisation, for the radius of each spot is a measure of the radius of the sphere at whose surface its vector terminates. The differences in size serve as a constant reminder that we are dealing with concentric spheres. To find the $\overline{QRS}-\overline{T}$ angle, we need only

TABLE I

	X		Y		Z		Magnitude m.c.v.s.	Longitude	Latitude
	Plani- meter reading	m.c.v.s.	Plani- meter reading	m.c.v.s.	Plani- meter reading	m.c.v.s.			
\bar{P}	83	20	-96	-24	-84	-21	40	45°	37°
\overline{QRS}	273	68	74	18	263	65	94	-44°	-11°
\bar{T}	-140	-35	-170	-42	41	10	55	-104°	50°
\overline{VG}		33		-24		76	86	-66°	16°

Planimeter reading of 401 = 100 microvolt-seconds (m.c.v.s.).

measure the arc distance between these spots. A moveable meridian is employed. This is a metal ring, whose inside diameter is equal to that of the sphere. It is graduated from 0° to 180° in both halves as in fig. 1b. The meridian is passed over \overline{QRS} and \bar{T} and snugly fitted to the sphere. In this position it bisects the sphere and thus encloses a great circle. If the 0° mark is placed over \overline{QRS} , the angular distance between \overline{QRS} and \bar{T} is read at \bar{T} in degrees. The angle in this case is 121°. It can also be measured by a snug-fitting semi-circle, a pair of dividers, or by a graduated string. If stretched between two points the string assumes the great circle position. An air-distance globe may also be used. This lies within a stationary horizontal meridian. To determine an angle between two points, the globe is rotated so that the arc between the points is aligned with the meridian.

The relationship between the axes of \overline{QRS} and \bar{T} is not sufficiently described by the magnitude of the \overline{QRS} - \bar{T} angle alone. It is necessary to determine the course, direction, or bearing of \bar{T} from \overline{QRS} . Two points, A and B, are shown on the sphere of fig. 4. They are joined by an arc of a great circle, AB. This is the shortest distance between these points and is analogous to a straight line on a plane. If a ship positioned at A were destined for B, its navigator would set a course from A to B. Every point on a sphere has its meridian. That of A is 75°. The bearing of B from A is the acute angle subtended by the arc AB and the 75° meridian. As the ship would sail in a southwesterly direction, its course, or bearing, at A is SW50°. This means that it is directed southwest at an angle of 50° with the meridian of its position. The bearings of angles shall here be based on the temporal sequence of the forces generated. Thus, as \bar{T} is inscribed after \overline{QRS} , the bearing of the \overline{QRS} - \bar{T} angle is from \overline{QRS} to \bar{T} . The \overline{QRS} - \bar{T} angle may then be given as (121°, SE41°, i.e., the axis of \bar{T} subtends an angle of 121° with the axis of \overline{QRS} and is southeast of \overline{QRS} , and the arc between \overline{QRS} and \bar{T} forms an angle of 41° with the meridian of \overline{QRS} . To complete the description, the position of \overline{QRS} should also be given, longitude being placed before latitude. As this is (-44°, -11°), the \overline{QRS} - \bar{T} angle is noted as (121°) (SE41°) (-44°, -11°) (angle, bearing, position).

If the duration of excitation were constant for the entire myocardium, the course of regression would duplicate that of accession, and T would be the mirror-image of QRS. The integrals of the forces generated, as represented by



Fig. 3a

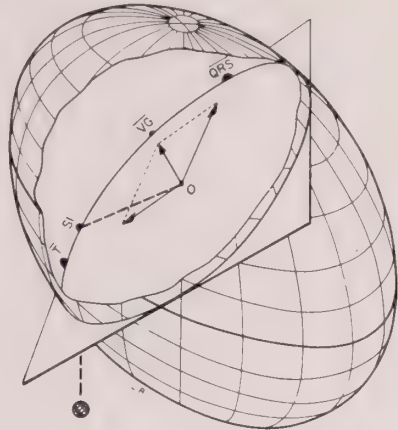


Fig. 3c

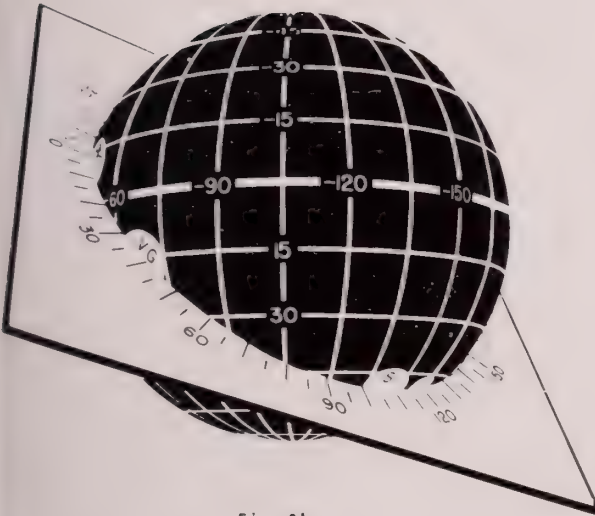


Fig. 3b

FIG. 3a. The axes of \overline{QRS} , \overline{VG} , and \overline{T} are represented by spots on the surface of a sphere. The radius of each is proportional to the magnitude of the vector it represents. The angles subtended by the vectors equal the arc distances between the spots. (Sphere photographed from back.)

FIG. 3b. \overline{QRS} and \overline{T} subtend a plane, which contains \overline{VG} , the plane of mean ventricular activity (Plv). S1 marks its slope. The dial is that of the moveable meridian when positioned for measurement of the $\overline{QRS-T}$ angle.

FIG. 3c. Plane of mean ventricular activity as seen from the first quadrant (above and in front). It passes through the center of the sphere and cuts off a great circle, on which the axes of \overline{QRS} , \overline{T} , and \overline{VG} pierce the surface of the sphere. The parallelogram of forces of Wilson's equation is inscribed on this plane. If a ball were placed at the center, it would roll down the line of maximum inclination of the plane. This is its slope. It is shown as an interrupted line and pierces the sphere at the point annotated as S1.

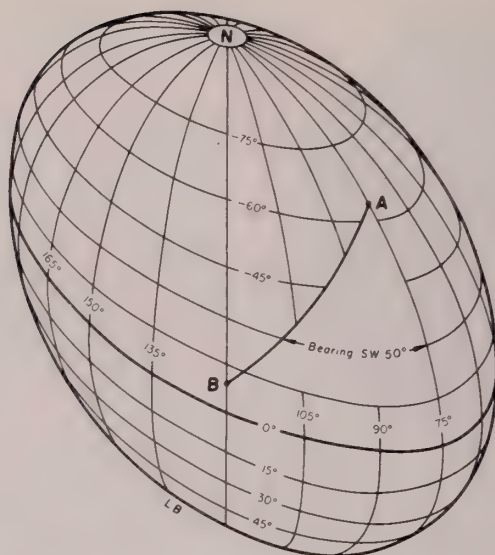


FIG. 4. The bearing of B from A is the acute angle between arc AB and the meridian of A.

the vectors, \overline{QRS} and \bar{T} , would be equal and opposite, and the $\overline{QRS}-\bar{T}$ angle, 180° . However, there are always differences in duration of excitation. The vector representing the integral of the forces produced by these differences is the ventricular gradient, \overline{VG} . \overline{QRS} and \overline{VG} are independent forces; \bar{T} is merely the mirror-image of \overline{QRS} as modified by \overline{VG} . The inter-relationships of these three forces are amplified elsewhere (9). When the mean difference in duration of the excited state is equal to zero, \overline{VG} is zero, and the $\overline{QRS}-\bar{T}$ angle is again 180° . Should \overline{VG} be other than zero but oriented on the \overline{QRS} axis, the $\overline{QRS}-\bar{T}$ angle is either 0° or 180° , depending on the magnitude and sense of \overline{VG} . However, when \overline{VG} deviates from the axis of \overline{QRS} it forces \bar{T} away from this axis so that the $\overline{QRS}-\bar{T}$ angle lies between 0° and 180° , and a plane is subtended by \overline{QRS} and \bar{T} , which contains \overline{VG} . \overline{QRS} , \overline{VG} , and \bar{T} therefore lie on a plane which may be called the *plane of mean ventricular (electrical) activity* and annotated by the symbol, Pl_v . In determining the $\overline{QRS}-\bar{T}$ angle, the meridian was imposed on this plane. It is illustrated in fig. 3b. As in fig. 3a, the posterior aspect is shown as the vectors involved pierce the sphere behind the frontal plane. Let us examine the cutaway representation of the mean plane of ventricular activity as seen from quadrant I (above and in front), the usual position of the observer (fig. 3c). It passes through O, the center, and cuts off a great circle, on which the axes of \overline{QRS} , \overline{VG} , and \bar{T} pierce the surface of the sphere. The vectors are represented by arrows whose lengths are proportional to their respective magnitudes. Note that the spatial parallelogram of forces of Wilson's equation, $\overline{VG} = \overline{QRS} + \bar{T}$, is inscribed on this plane.

In analyzing the various planes of the cardiac cycle, others of which shall be described below, it is useful to adopt some scheme by which these may be identi

fied and visualized. A plane passing through the center of a sphere may be represented by a single point on the surface of the sphere. This is the axis of its slope. A slope is that line on a plane which bears the maximum inclination to the horizontal plane. A ball placed at the center of the sphere will roll down the slope and pierce the sphere at a point whose geographical coordinates completely determine the plane. It is easy to visualize a plane from its slope by picturing this rolling ball.

The plane cuts off a great circle, and naturally the ball will roll towards the lowest point of this circle. This lies below the equator at the point of tangency of the circle and a parallel of latitude. The slope of the plane of mean ventricular activity is therefore readily determined. When the moveable meridian is in position for measurement of the $\overline{QRS}-\bar{T}$ angle, a mark is made on the sphere at the southernmost point or "southern vertex" of the meridian. The longitude and latitude of this point represent the axis of the slope.

In fig. 3c, the path of the rolling ball, or the slope of Pl_V , is shown as an interrupted line. Sl in this and the other figures represents the axis of the slope. Its coordinates are longitude, -143° ; latitude, 50° . These coordinates also describe the plane in what may be considered a more vivid manner. In figs. 3a and b, the arc between \overline{QRS} and \bar{T} , which may be taken as the edge of the plane, subtends an angle of 50° with the equator. This is the inclination, or dip, of the plane and equals the latitude of Sl . The great circle of the arc intersects the equator at two points. The ball will roll down an axis perpendicular to the diameter between these points. The longitude of the slope is therefore 90° from that of the intersection of arc and equator. By inspection of the intersection the plane may therefore be described as one that dips 50° from the horizontal in the direction of the -143° meridian of longitude. As the latter is called the bearing, Pl_V is that plane whose bearing and dip are -143° and 50° . Given a slope as a point on a sphere or by its coordinates, a plane is readily described and visualized in these terms.

It was stated above that \overline{QRS} and \overline{VG} are independent forces. \bar{P} is the third such force of the cardiac cycle. The inter-relationship of the three is expressed as the spherical triangle of fig. 5a, which may be called the triangle of the *independent forces*.

The instantaneous spherical coordinates of the entire cardiac cycle are supplied by the orthovectorcardiogram (see part I) (10). The instantaneous vectors of the spatial loops may therefore be positioned on the surface of the sphere to form what may be referred to as a *spherical vectorcardiogram*. Those of QRS are shown in fig. 6a and are to be visualized as radiating from the centre. In so doing they approximate a plane, which may be marked on the sphere by appropriate positioning of the meridian. This is the *mean plane of QRS*, (Pl_{QRS}). Its slope, as shown in fig. 6b, is $(-142^\circ; 52^\circ)$. The similarity to Pl_V is coincidental.

The radiating instantaneous vectors of the P and T loops also subtend mean planes (Pl_P and Pl_T). These are drawn as great circles on the sphere, and each is annotated by the coordinates of its slope. The relationship between two planes may be expressed by the magnitude and bearing of the dihedral angle subtended

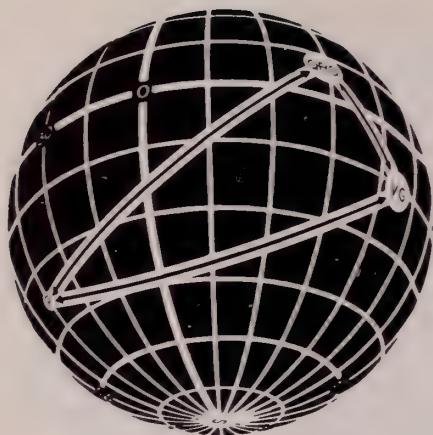


FIG. 5a



FIG. 5b

FIG. 5a. Triangle of the independent forces.

FIG. 5b. The relationship between two planes is expressed by the magnitude and bearing of the dihedral angle subtended by them. This is determined by measuring the arc perpendicular to both planes.

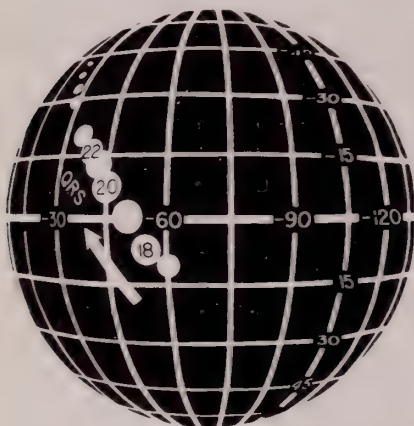


FIG. 6a

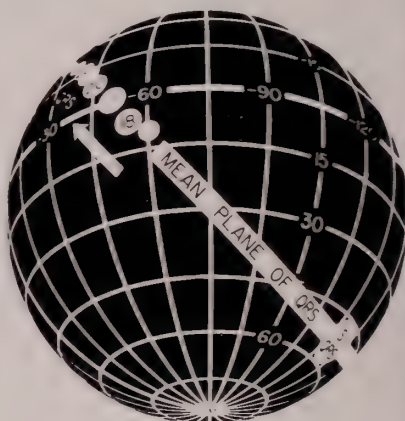


FIG. 6b

FIG. 6a. The instantaneous axes of the QRS loop. (Spherical vectorcardiogram).

FIG. 6b. The mean plane of QRS (Pl_{QRS}). Its slope is $(-142^\circ; 52^\circ)$ (bearing and dip). The rotation of the loop in space is (NW) $(-142^\circ; 52^\circ)$, i.e., it rotates in a northwesterly direction on a plane whose bearing and dip are -142° and 52° .

by them, as described for the $\overline{QRS}-\bar{T}$ angle. These are determined by measuring the arc distance between the great circles of the planes as in fig. 5b.

DISCUSSION

In the presence of a normal QRS, the physiological orientation of the ventricular gradient roughly parallels that of \overline{QRS} . When regions of the myocardium are influenced by ischemia, drugs, electrolyte imbalance, etc., the gradient vector is so affected as to point away from the involved areas. An angle is therefore formed between \overline{QRS} and \overline{VG} , the $\overline{QRS}-\overline{VG}$ angle, which may be used as

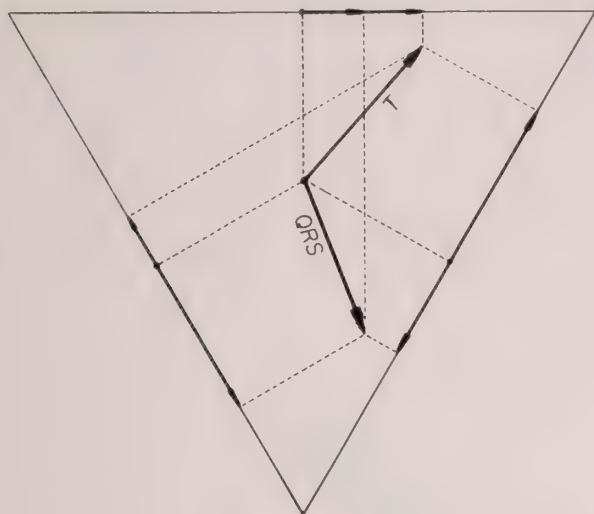


FIG. 7

an index of local disturbance. As \bar{T} equals \bar{VG} minus \overline{QRS} , it is also affected under these circumstances and subtends an angle with \overline{QRS} , the $\overline{QRS}-\bar{T}$ angle. It has been found empirically that an inverted T following a normal QRS in certain leads is indicative of myocardial damage. Such inversion results from deviation of the course of regression from that of accession. The $\overline{QRS}-\bar{T}$ angle is the measure of this deviation and equals the difference in orientation of the integrals of the forces generated by the two processes. In fig. 7, two vectors \overline{QRS} and \bar{T} , lying on the frontal plane and subtending an angle at the center of an Einthoven triangle, are resolved into their triaxial linear components on the sides of the triangle. \overline{QRS} and \bar{T} are discordant in leads II and III and concordant in lead I. The concordancy of each is dependent upon the inter-relationship of the axis of the lead and the magnitude and orientation of the angle. Since the same considerations apply when vectors and lead axes are off the frontal plane, the $\overline{QRS}-\bar{T}$ angle in space determines concordancy in any linear tracing regardless of the orientation of its axis of derivation. The relative positions (and sizes) of two spots on a sphere may therefore be taken as a net expression of T wave formations in all surface electrode leads, hence of myocardial involvement. To the extent that the angular distance and bearing of \bar{T} from \overline{QRS} are selectively affected by those conditions that alter T, the $\overline{QRS}-\bar{T}$ angle will be specific for such conditions.

Rotation is an important diagnostic criterion (11-21). In the normal subject the horizontal projection of the QRS loop is directed to the left, somewhat posteriorly, and shows counterclockwise rotation (14, 17). In right ventricular hypertrophy it is to the right, anterior, and shows clockwise rotation (12, 13, 15, 17, 18, 20, 21). It is not unreasonable to speculate that this reversal of orientation from left-posterior to right-anterior is accompanied by a turning over of the plane of the loop so that counter-clockwise rotation of its horizontal projec-

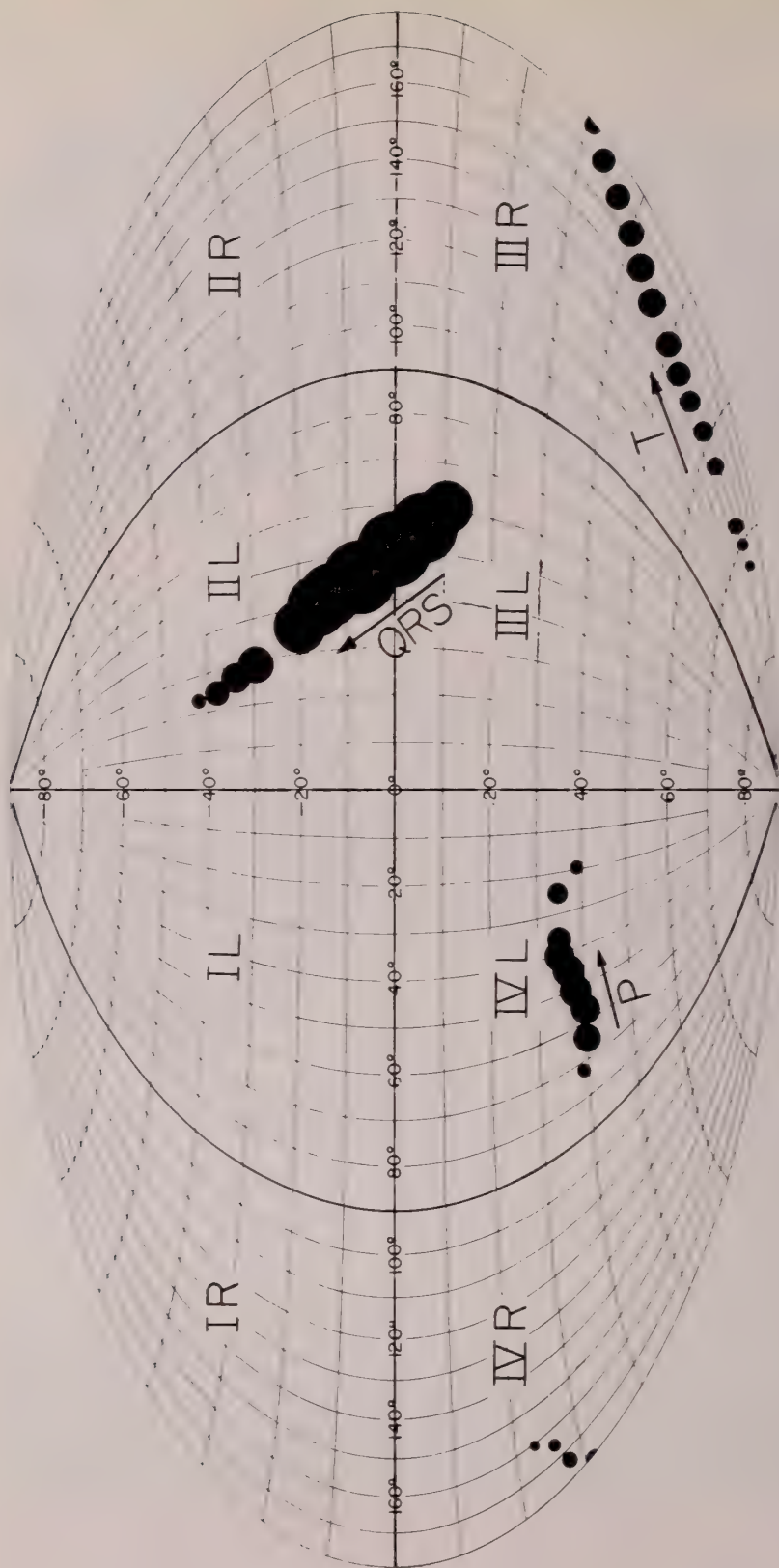


FIG. 8

tion is converted to clockwise rotation. During this turning over a position is reached at which the plane is perpendicular to the horizontal plane and may be considered as a meridian of the sphere. Its slope is therefore at the south pole, and the progressive turning of the plane, in the presence of pathology that predispose to right ventricular hypertrophy, may be followed by means of its slope, which may be pictured as a point on the sphere that slowly traverses the south pole. Rotation upon the cardinal planes depends upon rotation in space. This is readily visualized from the spherical vectorcardiogram and may be expressed in terms of its plane and course. Thus, as the loop in fig. 6b rotates in a north-westerly direction on a plane whose bearing and dip are -142° and 52° , its rotation may be noted as (NW)(-142° ; 52°). These figures also indicate the orientation of the loop, i.e., anterior or posterior, and are independent of the position of the observer. However, if the latter be arbitrarily fixed at the north pole, the rotation may be described as counter-clockwise on a plane whose bearing and dip are (-142° ; 52°).

The surface of a sphere is not developable, but cartography offers many methods by which it may be projected onto a flat surface, each of which is an approximation designed to a specific purpose. Aitoff's equal area projection, or the familiar egg-shaped map, is employed in fig. 8. It is probably the simplest method of representing the spherical vectorcardiogram with least distortion. The (anatomical) left half represents the posterior hemisphere; the right, the anterior. The spatial octants are indicated. This chart may also be used for statistical purposes and can be obtained from the U. S. Coast and Geodetic Survey, Washington, D. C. at a cost of 15 cents (§ 3099).

APPENDIX

on Tortuosity

The moving vector terminus in its excursion through space functions as the generatrix of a tortuous curve and defines the perimeter of the ruled surface generated by the vector. The tortuosity of the curve is a measure of deviation of the ruled surface from its mean plane. To determine the tortuosity of the QRS loop, the moveable meridian is positioned on Pl_{QRS} , and the maximum deviation of the QRS pattern is measured on each side with a pair of dividers. Tortuosity then equals the sum of the two values in degrees. Tortuosity of segments of the loop may be similarly obtained.

on Velocity

The velocity of the generatrix is a vector quantity equal to the speed of the generatrix directed along a tangent to the curve in the sense at which it is moving. The mean velocity for any time interval may be determined if the segment inscribed be small enough to render it essentially equal and parallel to its chord. The vector of velocity then equals the vectorial difference between the final and initial vectors of the segment. The subtraction is performed on the projections of these two vectors, and, after determination of the spherical coordinates of the

difference, the vector representing mean velocity of the interval may be shown as a spot on the sphere, at whose center it is considered to originate. It lies on the plane of the initial and final vectors, and this fact may be used to check its position. Magnitude of velocity is, of course, expressed in microvolts per time unit.

Angular velocity is also a vector quantity. Its determination requires no reservation as to length of segment of the curve. It is a measure of the velocity at which a line generator, the instantaneous vector, alters its orientation, or the velocity at which the spot on the sphere moves in passing from initial point to final point of a chosen time interval. The arc distance between the points is measured; it equals the magnitude of the angular velocity, or angular speed, and is expressed in degrees per time unit. The direction is that of a tangent to the arc midway between the points, and the sense, from initial point to final point. To represent angular velocity by a spot on the sphere, the vector may be considered as transferred to an axis passing through the center of the sphere and parallel to the tangent. To perform the transference on our material sphere, the moveable meridian is positioned over initial point and final point, and a mark is made on the sphere 90° removed from the mid-point of the measured arc. This is then expanded to a spot representative of angular velocity. As magnitude is measured also by the meridian, the three spherical coordinates of angular velocity are determined in one operation. Mean angular velocity for an interval embracing several recorded instants may be determined with the aid of a distance wheel. The vector then lies on the mean plane of the instantaneous vectors. The mean angular velocities for substantial portions of the loop may be obtained in this manner.

It should be interesting to subject the various classes of infra-nodal conduction abnormalities to such analysis.

on $\overline{QRS}-\bar{T}$ Angle

An angle subtended by two vectors, e.g., the $\overline{QRS}-\bar{T}$ angle, can be determined by construction. \overline{QRS} , \bar{T} and the line joining their termini form a triangle in space. Its frontal and horizontal projections can readily be drawn and the true length of each side determined by revolution. As three sides are then known, it can be constructed in its true size with the aid of a compass, and the $\overline{QRS}-\bar{T}$ angle thus obtained.

on Lead Axis Derivatives

To determine the derivative of a vector in space on any lead axis, these are positioned on the sphere and the subtended angle measured. The vector is then drawn on paper in its true length, deviated from the axis by the angle determined, and a perpendicular dropped from its terminus to the axis. It is obvious that if the angle exceeds 90° , the derivative will be negative. The conditions, suppositions, and limitations of this procedure will be apparent to the vector-cardiographer.

on Space-polar Coordinates

Given a vector as a point on the surface of a sphere, its angular space-polar coordinates (angles F, S, X, Y and Z) are found by measuring the arc distances between the point and these planes and axes.

on Angle Subtended by a Vector and a Plane

To determine the angle subtended by a vector and a plane, e.g., that between the integral of the initial component, \bar{Q} , and the mean plane of the body of the loop, the axis is represented on the sphere by a point and the plane by a great circle arc. The perpendicular arc distance between point and great circle arc then equals the desired angle.

on Bearing

In fig. 4, the north pole (N) and points A and B form a spherical triangle. NA and NB are the respective complements of the latitudes of A and B, or their co-latitudes. The angle at N is equal to the difference in longitude of A and B. As two sides and one angle are known, and as the lengths of the sides are expressed in degrees, the angular distance and course of B from A may be calculated from the law of sines:

$$\frac{\sin \text{angle at A}}{\sin \text{NB}} = \frac{\sin \text{angle at B}}{\sin \text{NA}} = \frac{\sin \text{angle at N}}{\sin \text{AB}}$$

The triangle may also be solved by the usual methods of great circle sailing or by the projection method of spherical trigonometry. The application of cartography is subject to the error inherent in all forms of map projection. The interested reader is referred to appropriate texts.

Annotation of bearing in terms of the great circle principle is geometrically correct. By definition, an angle is the amount of turning necessary to bring one line into coincidence with another. The great circle bearing is the course this line would take at its position to arrive at its destination via the shortest route, i.e., by generating a plane. With the sphere before us it is easily followed and readily visualized from its annotation (which must take into account position and angular distance). Under certain conditions, however, it poses a paradox. If the initial point be at long. 15°; lat. 15°, for example, and the final point at long. 150°; lat. -15°, we think of the final point as being northwest of the initial point, or in anatomical terms to its right and superior. By the great circle route, however, its bearing is southwest, i.e., the initial point starts its voyage in a southwesterly direction in order to arrive at the final point by the shortest route. It may be preferable therefore to refer one vector to another in terms of differences in longitude and latitude. Thus the final point is noted as W135°; N30° of the initial point.

on Magnitude

It is proposed above to indicate magnitude by the radius of the spot. Magnitudes of vectors can then be directly compared by linear measurement. In view-

ing such spots, however, we are inclined to correlate magnitude with size, or area. To represent vectors of widely differing magnitudes, moreover, the greatest spot must be enormous if the smallest is to be seen at all. It may be preferable, therefore, to represent magnitude by area. This entails no extra work.

If X = magnitude
 and Y = radius of spot such that its area
 is proportionate to magnitude
 then $Y^2 \sim X$.

If the curve of $Y^2 = X$, be drawn, the radius of the spot for any value of X is equal to the corresponding ordinate. An alternate method is to represent magnitude by the length of a straight line (great circle arc) whose mid-point lies on the point-representation of the vector axis.

SUMMARY

1. A method of representing spatial vectors by points on the surface of a sphere is presented.
2. The angles and planes subtended by the forces generated during the electric cycle of the heart are discussed.
3. A simple means of determining these is advanced.
4. Schemata by which they may be fixed, visualized and annotated are proposed.
5. These are applied to velocity, tortuosity and rotation in space.

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A PSYCHIATRIC UNIT IN A GENERAL HOSPITAL*

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A psychiatric unit in a general hospital will function primarily in terms of its basic philosophy. This in turn is in part related to the philosophy of function of the particular general hospital in which it finds itself. There are many types of general hospitals subserving different functions in relation to the particular community in which they are located. Although there is a general overlapping of function which is central to all general hospitals, nevertheless each type has a certain uniqueness and specificity, and therefore from this point of view each psychiatric unit will of necessity be somewhat different from any other psychiatric unit in another general hospital.

The primary purpose of any hospital is to be of service to individuals who are ill. This is at the core of its function. Nevertheless, depending upon geographic area, the community resources, the culture of the community and locality have an impact on function. There is an immediate difference between a general hospital set up primarily for the diagnosis and treatment of individuals with chronic disease and one which is set up primarily for the diagnosis and treatment of acute illness. There is a difference between a so-called university hospital subserving an undergraduate medical school program and one that has no responsibility for the teaching of undergraduates. The type and character of residency training programs will influence the hospital's function if for no other reason than the selectivity of case material. Whether a hospital serves primarily as a local hospital or a medical center will also determine the character of its function. In addition, with sociological and economic changes taking place at the present time and some alterations in some of the basic ideas as to the role of a hospital in the community, some hospitals are expanding their role into areas of public health and prevention, and this in turn influences the character of the professional job that needs to be done. Then again, the orientation towards research has a tremendous impact on the hospital.

The size and very character of a psychiatric unit in a general hospital is a result of the factors above stated, in addition to many others. In the decade between 1945 and 1955 over 550 general hospitals instituted psychiatric units as part of their function. Naturally these consisted of varying patterns. The philosophy of the psychiatrist in relation to his profession and his visualization of his role within a general hospital will actually play a significant part in what kind of psychiatric unit is built up.

As is well known, the psychiatrist and psychiatry for many years was isolated in a specialty hospital and therefore dealt with only one aspect of the psychiatric problem—those patients who were ill specifically with a psychiatric syndrome.

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The psychiatrist in private practice in his office or specialty hospital that he utilized broadened his patient base quantitatively but not necessarily qualitatively since he continued to deal with patients in certain diagnostic categories. Again in recent years an old conceptual framework was refurbished under the term psychosomatic medicine. This further broadened the area in which the psychiatrist as a psychiatrist and physician became involved. Unfortunately, in many instances the psychiatrist's contribution was more in the realm of certain theoretical formulations rather than direct clinical practice. This statement is intended in no way to devalue the psychiatrist's contribution to this field. It was only when the psychiatrist entered the general hospital in his role as a physician that a vast new area of function became evident.

The psychiatrist as a psychiatrist has and is making a contribution to medicine. Psychiatry as a basic science is even more significant, and it is in this area of basic science that psychiatry's role is of the utmost importance in a general hospital. Limitations of time do not allow for a complete elaboration of the wide role of the psychiatrist in the general hospital. The above serves as pertinent illustrations.

Within the above framework therefore the psychiatric unit of The Mount Sinai Hospital was organized. Organization and function are intimately related. To this audience it is unnecessary to emphasize that when one talks of a Department of Psychiatry that one includes not only the psychiatrist, but the social worker, the psychologist, the occupational therapist, and other adjuvant personnel, each functioning in their appropriate role, and all members of a diagnostic and therapeutic team. For the purposes of this presentation a simplified description of the organization of the service will be presented.

As already stated, there are at least three aspects to a psychiatric unit in a general hospital: service, education, and research. Therefore, a psychiatric department must be organized in order to fulfill the essentials of these three functions. One is immediately confronted with a problem in relation to the service aspects of a psychiatric unit. Limitations of space and time are reflected in the necessary choice as to whether the psychiatric unit will be oriented primarily in service to the general hospital population or the community in which the hospital is located. This is no academic question, since any psychiatric facility is under constant pressure from the community it serves. Here again the basic philosophy of the psychiatric service in relation to its function will determine the choice.

Since psychiatry is a service that is related to every aspect of the practice of medicine, since education is an important part of its function in relation to the general hospital and its staff, and since education is only possible under circumstances where the psychiatrist demonstrates his value to the surgeon and the internist in relation to their problems, it becomes clear that the choice must always be in terms of service to the hospital population primarily rather than to the community outside of the hospital.

The organization of the psychiatric unit in a general hospital may be divided roughly into two general areas, the smaller of which deals with patients in its own ward service and outpatient clinics. This is only an apparent paradox, and

what is meant by this above statement is simply that the patients that are referred directly to a psychiatric ward from other parts of the hospital are those patients who require the diagnostic and therapeutic facilities that are primarily psychiatric. The psychiatrist in order to fulfill his necessary function in a general hospital has of necessity to work in other departments of the hospital. At The Mount Sinai Hospital this has been implemented through our liaison service which will be discussed below.

Of the facilities under its own direct jurisdiction, the psychiatric outpatient is of wider importance. Here again a choice in terms of quality rather than quantity has to be made. Where the emphasis is on psychotherapy, a minimal time must be allowed for each patient's interview. The clinic must be divided in such a way that they meet more than once a week in order to permit a patient to be seen by his physician at least twice a week when necessary. Our own adult outpatient department has four clinic units, two for general psychotherapy, one is a special clinic for group psychotherapy which combines service, education, and research in that area, and the fourth clinic, manned primarily by resident and attending staff. The function of this last clinic is to enable the resident to follow his own patient that he has worked with on the inpatient service when that patient is discharged.

Education, especially in medicine, is a continuing process, as we all know. Therefore, opportunities must be presented to the attending staff for such a continuing process. In relation to the outpatient staff it becomes necessary to provide for work under supervision, and this is provided for by the chiefs of clinic. In addition each unit should have at least one teaching conference per week. Such supervision and conferences take away from the limited time available, but nevertheless are the quid pro quo for the staff members for which there can be no substitute. Incidentally, a staff member working in the outpatient must give a minimum of six hours per week in order to maintain his staff appointment.

It is essential that a psychiatric department in a general hospital have available a number of beds as an inpatient service. The actual number of beds in any given unit will vary, for many reasons related to the size of the hospital and particularly to the number of ward beds on other services. Generally, a minimum of eight beds are necessary. In our own department we have 21 inpatient beds for adults and several inpatient beds for children in relation to some 550 service beds for the other departments. The function of these ward beds is of great interest. Since they are utilized primarily for the hospital population, the spectrum of diagnostic categories is of interest. In a previously published paper, the following categories were listed as the census on a particular day:

"1. Ulcerative Colitis

Psychoneurosis (obsessive-compulsive with depressive features).

2. Ulcerative Colitis

Mental deficiency (obsessive-compulsive personality).

3. Manic-Depressive (depressed, hypochondriasis).

4. Essential Hypertension

Schizophrenia, catatonic.

5. Anorexia Nervosa.
6. Fugue State, questionable catatonic schizophrenia.
7. Ulcerative Colitis
Obsessive-compulsive personality.
8. Diabetes Mellitus
Psychosis with depression and paranoid trends.
9. Postgastrostomy
Hysterical personality type.
10. Psychosis (paranoid state, somatic delusions).
11. Ulcerative Colitis
Schizophrenia, type unclassified.
12. Coccygodynia
Psychoneurosis, conversion hysteria.
13. Duodenal Ulcer—postvagotomy and gastroenterostomy
Passive-dependent personality.
14. Duodenal Ulcer
Passive-dependent personality in adolescent boy.
15. Rheumatoid Arthritis, Amyloidosis
Psychoneurosis, obsessive-compulsive.
16. Hyperthyroidism
Chronic anxiety state.
17. Gastric Ulcer—postvagotomy and gastroenterostomy
Psychoneurosis, hysteria.
18. Psychoneurosis (conversion, cardiac symptoms)."

These diagnostic categories perhaps are the best indications of how a psychiatric unit functions in a general hospital.

It cannot be overemphasized that a psychiatric department in a general hospital must be completely integrated with the overall function of that hospital. There have been psychiatric divisions in general hospitals for many years. However, by and large they functioned as if they were only geographically located in the hospital without any real relationship to the primary purpose of the general hospital. Geographical location and functional operation may be two completely different things. As a matter of fact the more a psychiatric department busies itself with patients whose primary diagnostic categories fall within the sub-specialty of psychiatry, the less are its chances of being part of the operation of the general hospital.

I have stated elsewhere that the primary function of a psychiatric unit in a general hospital is not to diagnose and treat schizophrenias, manic-depressives, etc. as such, but to participate in the psychiatric problems of the patient load throughout the hospital. One effective technique that has been developed at The Mount Sinai Hospital is the division of liaison psychiatry. Every service in the hospital has a psychiatrist or team of psychiatrists, depending upon its size, attached to it. These psychiatrists while members of the Department of Psychiatry and responsible to it nevertheless function as a team member of the service to which they are assigned. The liaison psychiatrist has multiple roles to play. In part, he is the consultant to his service. In part, he functions as a teacher

for the attending staff and residents, and in part he serves not only as a diagnostician but also works therapeutically with patients in relation to problems associated with their illness or procedures to be carried out. As an illustration, he may function in relation to the emotional problems associated with a pre-operative situation and follow the patient through the necessary surgical intervention. The liaison psychiatrist in addition to the above roles also functions as a referral physician for the Department of Psychiatry. Only those patients that require the special diagnostic and therapeutic measures which are available only on the psychiatric service are referred to that service. It is intended that the patients remain as far as possible on the parent service to which they are admitted.

The role that the liaison psychiatrist plays in a general hospital is an exceedingly complex and important one. In many ways this is the most significant area in the relationship of psychiatry to medicine as a whole as it is practiced in a general hospital. A study that is progressing at the present time in relation to the types and categories of patients seen by the liaison psychiatrist is of great interest. The variety of patients seen by the psychiatrist in one or the other of his roles and the spectrum of diagnostic categories into which they fall is again an index of the psychiatrist's role in modern medicine. In addition to the liaison group in the inpatient service, there is a team of liaison psychiatrists that function in relation to the outpatient clinic.

It has already been stated above that a teaching program for the attending staff and interns and residents on services other than psychiatry is an important function of the liaison service. We have found that an exceedingly flexible program with variations is necessary. This flexibility and variability relates to each service and sometimes to each ward. The details of this training program will be reported in extenso at some future time.

In the study referred to above, there are indications of the roles that the liaison psychiatrist is called upon to play and the kind of assistance that is requested from him in the management of the patient. In a two year study of 2309 consultations, the breakdown revealed that in 61.4 per cent the problem was one of differential diagnosis; in 26.8 per cent the problem was frankly psychiatric in the sense of schizophrenic reactions, suicidal tendencies, etc.; and 11.8 per cent of the requests were for assistance in the total management of the case.

The disposition of these cases is also of interest. One hundred forty-four were transferred to the adult psychiatry ward; 408 were referred to the psychiatric outpatient clinic; 825 received psychotherapy on the parent ward; 340 were referred to social service; 98 were transferred to state hospitals; and in 494 there were no specific recommendations, disposition or psychopathology.

One minor but significant finding was the timing of the consultation request. In this group of patients they were seen on an average of four days after admission. In the past the consultation request came most frequently near the end of the hospital stay after a negative physical work-up.

It should be stated that since the liaison psychiatrist is attached to the service as a member of the team, he does not have to wait to be called in but is free to

see the patients at any time he or anyone else on the service, whether interne, resident, attending, social worker or nurse, find indications for the psychiatrist's participation. In actual fact many of the consultation slips for our own records are frequently written by the psychiatrist himself.

In addition to a teaching role in relation to the members of the hospital attending staff and its interns and residents on other than psychiatric services, there is of course an all-important other role, and that is education and training for the psychiatric attending staff and its own resident staff. Education as we all know is a continuing process, and the staff membership of any department in a hospital consists of individuals with varying experience. A consistent pattern for our own education as members of the attending staff has gradually evolved. An important part of this pattern is the conference system.

The department is divided into some 20 functional units, each one of which is headed up by a chief of the unit. In the outpatient, the chief of clinic in one of his roles is responsible for the supervision of his staff in a teaching capacity. Each unit meets together in a conference at least once a week. These conferences conducted by senior members of the staff serve an important educational function. The department as a whole meets frequently in departmental meetings. Weekly there is what is called a liaison conference which originally consisted of the liaison psychiatrists throughout the hospital who met to discuss problems relating to their function. Gradually, however, this conference is being utilized for presentation-discussion of varied problems. Research projects in progress are presented here. Interesting clinical material, administrative problems, problems of theoretical significance are also presented for discussion, and a theme or topic may be presented and discussed over many meetings. This type of forum is of great value to our department.

The training of residents in psychiatry is an important function of a department in a general hospital. In our own case we are accredited for a two year training program in general psychiatry. Since we do not have the varied clinical material that is necessary for a complete training program in psychiatry, we have never set up a complete training program. Our residents are required to have at least one year and preferably two of previous training in psychiatry before being accepted in our program. In a sense we consider our training program to be a kind of a honing process. The emphasis is on training in psychotherapy and depends heavily on the preceptor system. The case load for the resident is a relatively small one, but since patients are seen daily, the overall work load for each resident is rather heavy. In addition to the training program in general psychiatry, there is a two year program for training in child psychiatry. Our close working relationship with the Departments of Pediatrics and Obstetrics makes this program a broad one and enables us to present to the trainee a somewhat unique opportunity.

It should be emphasized that the base for the training of a resident in psychiatry in a general hospital is much wider and the opportunities greater than those presented to the resident in a special psychiatric hospital. A psychiatric unit in a general hospital not only presents the opportunity of relating medicine to psy-

chiatry, but also of relating psychiatry to medicine. This is true at the resident as well as at the attending level.

I have discussed the service aspect and the educational aspect of psychiatry in a general hospital. In addition there is another aspect of the utmost significance and importance for medicine and psychiatry, and that is the type of research opportunity in this setting. Here again, the mere listing of some of the types of projects that have been carried on or that are in progress at the present time is an excellent index of the opportunity presented to psychiatry. Working in close relation to all aspects of medicine many questions and problems arise that can be answered only by appropriate research projects. The liaison psychiatrist in daily contact with the problems of the service in which he works is in the position of making a direct contribution towards the solution of these problems. The opportunities for collaborative research are many, and actually a large number of our studies are being done in this collaborative manner.

For instance, an opportunity presented itself over a period of several years to investigate patients with gastric fistulae. This project involved collaboration with the Departments of Surgery, Medicine, Gastroenterology, Physiology and Psychiatry and resulted in the publication of a series of papers which made some contribution to each one of these disciplines, in addition to raising some interesting questions in regard to methodology. The liaison psychiatrist working in the Departments of Neurology and Ophthalmology carried out a significant project relating to post-operative reactions of patients with cataracts. The same psychiatrist working collaboratively with the neurologists made some significant contributions to the problem of the organic brain syndrome.

The psychiatrists working in the Department of Surgery were able to study certain aspects of the pre-operative and post-operative reaction of patients. The liaison psychiatrist working with the radio-isotope group carried through an important project concerning hyperthyroid patients treated with isotopes. The fact that we have a respirator center at the hospital permitted a significant contribution by the liaison psychiatrist to its function, and some projects dealing with various aspects of psychoneurophysiology are being studied as a result of this opportunity.

The studies on perception in progress in the department as you all know are a major contribution to this field and have thrown light upon many problems in psychoanalytic psychology. Although this particular study might well have been carried out in another setting, nevertheless the fact that a psychiatric department is part of the general hospital setting permits a wider variation of subjects and collaboration with other disciplines where necessary to carry out various aspects of the project.

There are, of course, numerous problems of a research nature within the Department of Psychiatry itself, and our department is engaged in working in many areas. It is not my intent to list all the work that has been done or is being done, but to present a series of illustrations to demonstrate the unique potential for research offered by the presence of a psychiatric unit in a general hospital.

I have talked in terms of organization and function, of service, education, and research. All of these are significant and important. To me, perhaps the most important aspect of all is one that I have not as yet mentioned, and that is the fact that the psychiatrist working in a general hospital has again integrated himself with medicine as a physician. The humility with which he accepts this role is perhaps the best index as to how he fulfills his professional function as a psychiatrist in medicine.

A SIMPLE, RAPID TECHNIQUE FOR THE DEMONSTRATION OF L.E. CELLS

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AND

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The demonstration of L.E. cells is a time-consuming and exacting task. Incubation alone requires one to twenty-four hours; microscopic examination may be prolonged and fatiguing. In instances of low potency of the serum or when clinical suspicion is high but previous preparations are negative, a prolonged search may be necessary before the preparations are considered either positive or negative.

It appeared desirable to devise a method which is simple to perform, requires only a short incubation period and results in preparations which can be read quickly.

The method to be described is based on the observations of Snapper and Nathan that air-dried white cells provide an excellent substrate for the formation of L.E. cell inclusion bodies and further, that a highly positive preparation can be produced when the incubation period is as little as one hour (1).

The method devised consists in the use of white cells suspended in heparinized test plasma, one portion of which is spread on a slide, allowed to dry and provides a source of L.E. cell inclusion body substrate; the other portion of which is employed for phagocytosis of the inclusion bodies and the formation of L.E. cells. The incubation period is ten to fifteen minutes.

METHOD

Technique

1. Five to ten ml of venous blood is collected in a syringe which has been moistened with heparin in order to prevent clotting. The blood is placed in a clean test-tube and the cells allowed to settle. When two to four ml of plasma is clear of red cells, this portion is removed by pipette and placed in a serology or centrifuge tube and centrifuged until a button of cells is visible at the bottom of the tube. (The centrifugation is done slowly and should not require more than five minutes, since prolonged centrifugation at high speeds produces gross clumping of cells and prevents complete dispersion when resuspension of the cell button is performed.)

2. The supernatant cell-free plasma is removed by pipette until the volume of remaining plasma is approximately twice that of the button. The tube is then agitated gently until the button of cells is completely resuspended.

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3. One drop of the suspension, collected by pipette, is placed in the middle of a glass microscope slide and a square cover slip placed centrally on the drop and so positioned that two corners of the cover slip project over the long edges of the slide. Dispersion of the drop beneath the cover slip is rapid, and when complete the cover slip is removed by grasping a projecting corner and sliding the cover slip off the slide in a direction parallel to the surface of the slide.

4. Within one to two minutes the smear dries. It is necessary that the smear be completely dry before proceeding to the next step.

5. When the smear is dry, a second drop of the cell suspension is placed in the middle of the smear and again a square cover slip placed centrally on the drop. This time the cover slip is positioned so that the edges are parallel to those of the slide.

6. The preparation is now incubated at 37°C for ten to fifteen minutes in a moist medium. This is best done by placing the preparation in a Petri dish, the bottom of which is covered by one piece of moistened filter paper. The slide is placed on the filter paper, the Petri dish covered and placed in the incubator.

7. Following incubation, the preparation is removed and the cover slip taken off the slide. This is most easily done by placing a finger tip on one edge of the cover slip to prevent slipping and elevating the opposite edge with a No. 11 Bard-Parker blade. When the edge is elevated, the cover slip is flicked off the slide with the blade. Any excess plasma is removed by holding the slide in the perpendicular and tapping it gently on a hard surface. The ease with which the cover slip is removed is dependent on the positivity of the preparation. (See *Examination of the Preparation*)

8. When the slide is dry, it is stained by any one of the conventional methods used for blood smears. We have found the Jenner-Giemsa stain the most reliable.

To recapitulate: One drop of a concentrated suspension of white cells in the heparinized test plasma is spread on a slide and air dried. This drop furnishes the source of L.E. inclusion body substrate. A second drop of the suspension is then placed on the smear and quickly covered with a cover slip. The second drop provides viable white cells for the phagocytosis of inclusion bodies formed during the incubation. Following a fifteen minute incubation the cover slip is removed and the slide stained and examined.

A minor variation of the method allows the use of the patient's serum or plasma and the white cells of a donor. The procedure is identical except for step No. 2. At this point, all of the supernatant plasma of the donor specimen is removed and the donor white cell button is resuspended in the serum or plasma of the suspected L.E. The donor cells must not be leukemic unless there is a preponderance of mature granulocytes.

Examination of the Preparation

As with all the accepted methods of demonstrating the L.E. cell phenomenon, the criterion of positivity is the presence of L.E. cells. The finding of unphagocytized L.E. inclusion bodies is suggestive of positivity; however, artifacts resulting from nuclear disintegration may be confused with L.E. inclusion bodies and a preparation should not be considered positive in the absence of L.E. cells.

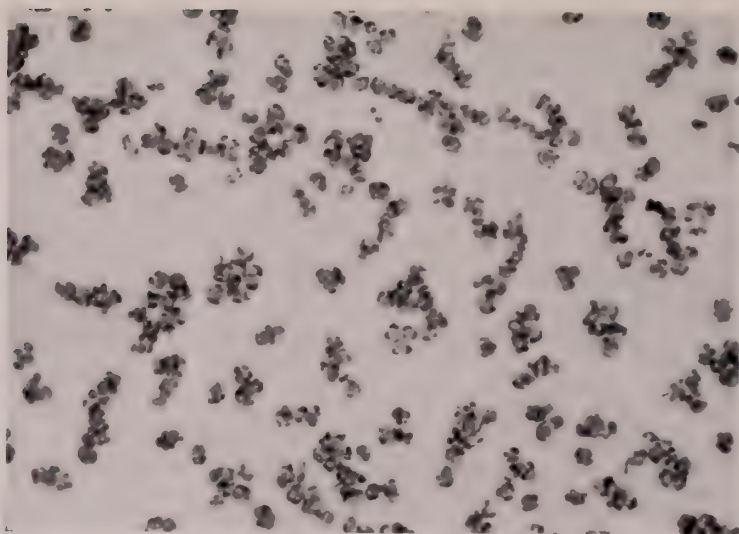


FIG. 1. L.E. Cell Preparation. $\times 190$.

Prior to the examination under the oil immersion lens several observations should be made:

A. Under Step 7 of the method, mention is made of the ease with which the cover slip is removed. Great variability is found depending upon the viscosity of the plasma layer between the slide and the cover slip. The cover slip is removed with difficulty when the plasma layer is highly viscous and tenacious and clings to the glass, or removed with ease if the plasma layer is of a relatively normal viscosity. It has been found that by comparing known positive and negative plasma, as determined by Lee's clot incubation method, the plasma of a positive preparation retains a relatively normal viscosity, whereas the plasma of a negative preparation is highly viscous and tenacious (2). For this reason careful observation during the removal of the cover slip is worthwhile. Similarly, gross examination of the slide after removal of the cover slip will disclose a smooth, thin sheen of plasma over a positive preparation and a corrugated gelatinous plasma layer over a negative preparation. Of several hundred preparations performed on about thirty different known positive plasma specimens, only one plasma specimen produced a corrugated surface. None of the negative specimens, about fifty, produced a thin non-corrugated surface. In several instances cover slips were removed with ease, suggesting positivity, while no L.E. cells could be found. In all, however, L.E. cells were eventually found in later preparations. This observation is admittedly highly subjective and is not offered as a substitute for L.E. cells.

B. The second observation concerns that of white cell clumping. We have noticed, as has Ziff, that clumping of white cells occurs characteristically in positive preparations (3). Negative preparations usually show a uniform dispersion of cells and in the areas where the plasma layer is corrugated the cells are found

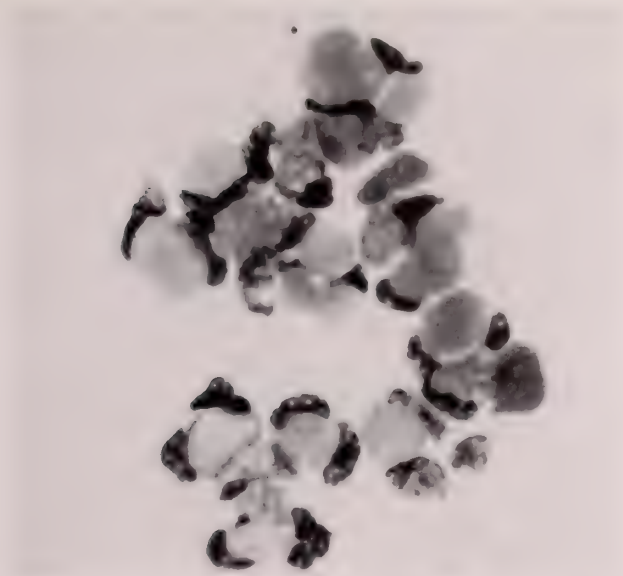


FIG. 2. Close up view of Figure 1 showing clumping of L.E. Cells. $\times 1000$.

to be concentrated but not clumped. The clumping phenomenon is not specific, but its presence is suggestive of positivity. Thus if the cover slip is removed with ease and clumping is present, even though L.E. cells are not found, the preparation should be repeated, since the combination is strongly suggestive of positivity.

C. Finally, it is frequently possible to recognize L.E. cells under the microscope at low power. Recognition at low power is facilitated by a background which contains only occasional red cells, ninety per cent of the cells being white cells and these sufficiently dispersed to allow fairly accurate identification of single cells.

Final identification of the L.E. cells must be done under the oil immersion lens. The appearance of L.E. cells produced by this method is similar to those produced by the accepted techniques.

Sensitivity of the Method

When highly positive plasma is used, detection of L.E. cells is rapid, since 70 to 90% of the cells are L.E. cells. As many as twenty L.E. cells may be seen per oil immersion field.

When weakly positive plasma is used the sensitivity of the method is comparable to that of the clot-incubation method as far as the formation of L.E. cells is concerned. However, even when only a few L.E. cells are found, the cover slip is removed with ease, the plasma layer is free of corrugation and white cell clumps are found. If the weakly positive plasma is progressively diluted with isotonic saline prior to performing the test, L.E. cells will eventually fail to appear, but further dilution is required before the plasma layer appears corru-

gated and tenacious and white cell clumping disappears. Thus these adjunct observations are extremely useful in determining how scrupulously the search for L.E. cells must be performed.

We have been unable to demonstrate loss of potency of the plasma when anti-coagulants are used.

DISCUSSION

The fundamental difference between this method and accepted methods lies in the treatment of the substrate cells (source of L.E. inclusion bodies). As noted by Snapper and Nathan, air-dried cells rapidly undergo transformation to L.E. inclusion bodies with proper treatment. We have not been able to demonstrate potentiation, that is, that air-dried cells undergo conversion to L.E. inclusion bodies when routine methods fail. The difference lies rather in the rapidity of conversion, less than ten to fifteen minutes as contrasted with one to twenty-four hours. A change in plasma viscosity probably occurs also when the routine methods are employed, but detection of this change is greatly facilitated by the need to separate glass surfaces coated by the plasma, when the cover slip is removed from the slide, and further verified by inspection of the plasma layer after the cover slip is removed. The alteration or absence of alteration of plasma viscosity apparently is related to cell breakdown occurring during incubation, since incubation of both positive and negative plasma without cells produces no obvious change from normal viscosity and the cover slips are removed with equal ease in both cases.

SUMMARY

A method is described for the demonstration of L.E. cells, employing heparinized plasma. One portion of the test plasma, containing white cells, is smeared on a glass slide, allowed to dry and acts as the substrate for the formation of the L.E. cell inclusion bodies. Another portion of the test plasma, containing white cells, is placed on the smear of cells and the preparation incubated for 10 to 15 minutes.

An additional criterion for positivity is described, that is, the negligible change in plasma viscosity noted in positive preparation as opposed to the striking increase in plasma viscosity noted in negative preparations.

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SURVIVAL FOLLOWING MASSIVE INTESTINAL RESECTION FOR EMBOLUS TO THE SUPERIOR MESENTERIC ARTERY

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A review of the records of patients with occlusion of the mesenteric arteries and veins with infarction of the bowel at The Mount Sinai Hospital in New York City was reported by Kirschner (1) in 1955. In that series there were twenty-seven patients with arterial vascular occlusion and none survived. Shortly after the publication of that report, a successful operation was performed at the same Hospital upon a patient suffering from an embolus to the superior mesenteric artery.

Because of the complicated postoperative course, and because of the problems involved in the management of this patient in both the immediate and late postoperative periods, this case is reported in detail.

CASE REPORT

A. S. (Unit #37857), a sixty-five year old white female, was readmitted to The Mount Sinai Hospital on May 24, 1955, only eight hours after her previous discharge. She complained of abdominal pain which began just a few minutes after leaving the Hospital that morning.

Her first admission was in November, 1954, at which time she had had bronchopneumonia. She then gave a history of symptoms of hyperthyroidism of many years duration. Radioactive iodine studies confirmed the presence of thyrotoxicosis. An electrocardiogram showed auricular fibrillation and digitalis effect. After the pneumonia had resolved, the patient was given a therapeutic dose of radioactive iodine. She was then discharged, and therapy with Lugol's solution was continued at home.

Her second admission on May 20, 1955, was for conversion of the auricular fibrillation. Quinidine was administered, and she reverted to normal sinus rhythm on May 23. Although a mild diarrhea developed while receiving quinidine therapy, the patient was discharged the following morning at ten o'clock. She was readmitted at six-thirty o'clock that evening because of severe, generalized, crampy, abdominal pain which began just after leaving the Hospital. The pain became steady and persisted, and was associated with nausea, anorexia, and vomiting. There was no obvious blood in the stool.

Physical examination revealed an acutely ill female with a temperature of 101°F. The blood pressure was 200/95, the pulse rate was 100 per minute and irregular, and the respirations, 16 per minute. The heart was not enlarged; the rhythm was that of auricular fibrillation, and a soft systolic murmur was heard over the precordium. The lungs were clear. The abdomen was silent and slightly distended. There was generalized tenderness, most marked in the right lower

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quadrant where a soft, exquisitely tender mass could be palpated. There was also spasm and rebound tenderness in that area.

The hemoglobin was 16 Gm. per cent and the white blood cell count was 20,000 per cu. mm., with a shift to the left. Urinalysis was negative, and examination of the stool showed a negative guaiac reaction.

Operation was carried out soon after admission. Under endotracheal ethylene and ether anesthesia, an exploratory laparotomy was performed. There was a small amount of sanguinous peritoneal fluid. The distal ileum was completely gangrenous. With the exception of the most proximal jejunum where a small vessel was seen to pulsate, there were no pulsations throughout the mesentery. There was no pulsation in the middle colic artery, but distal to this, one could feel arterial pulsation. Although the remainder of the small intestine was not frankly gangrenous, it became increasingly cyanotic during exploration.

It was apparent that a massive resection was necessary. The entire small intestine was resected, beginning proximally at about eighteen inches from the ligament of Treitz and continuing distally as far as the distal transverse colon. There was no arterial bleeding from any of the cut mesentery except at the points of transection of the bowel. Intestinal continuity was reestablished with an end to end anastomosis between the jejunum and the colon, using an outer layer of interrupted silk sutures and an inner layer of continuous chromic catgut. The mesentery of the jejunum was tacked to the mesocolon, and the abdomen was then closed with a single layer of figure-of-eight buried wire sutures. The skin was closed with interrupted silk sutures.

During the first forty-eight hours postoperatively, there were episodes of hypotension which responded to blood transfusions and vasopressors. Her temperature reached a high of 103.4°F. on the second postoperative day, then rapidly returned to normal. The abdomen remained soft; peristalsis returned on the second postoperative day, and the patient passed a large stool on the fourth postoperative day. Oral fluids were begun at that time. Except for a superficial abscess at the lower angle, the wound healed per primam. Penicillin and streptomycin were given for two weeks. The patient was given a high calorie, high protein, high carbohydrate, low fat diet, with supplemental oral and parenteral vitamins. During the first week postoperatively, she was apathetic and lethargic, and found it difficult to partake of food. The patient was having from four to ten loose bowel movements per day, and although tincture of opium and kaopectate lessened them somewhat, it was most difficult to control the diarrhea.

On the seventh postoperative day, it was noted that the patient was jaundiced, and blood studies showed that the bilirubin was 7.8 mgm. per cent; the alkaline phosphatase, 15.8 Bodansky units; the cephalin flocculation, 2 to 3 plus; and the protein was 7.5 Gm. per cent, with an albumin of 2.4 Gm. per cent.

There was little change in the general condition of the patient during the next two weeks. On June 19, the twenty-sixth postoperative day, she complained of severe pain in the right upper quadrant where physical examination revealed spasm, tenderness, and rebound tenderness. Her temperature rose to 102.6°F. There was no change in the degree of jaundice. It was felt that she had developed an acute cholecystitis and that laparotomy was indicated.

She was operated upon that evening. The gall bladder was enlarged, tensely distended, and filled with dark bile. There were no stones. The common duct was markedly dilated but contained no stones. Cholecystectomy and choledochostomy with T-tube drainage were performed. Culture of the bile revealed *Bacillus coli*.

The postoperative course was uneventful and the general status of the patient slowly improved. Her jaundice gradually decreased, and the T-tube was removed after a cholangiogram was proved negative. A gastrointestinal series, performed on July 11, showed that about eighteen to twenty-four inches of jejunum had been anastomosed to the distal transverse colon.

Although kapectate partially controlled the diarrhea, the patient was having from five to eight bowel movements per day when she was discharged on July 18. She remained at home, chronically invalided; and despite the administration of large doses of paregoric and kapectate, she continued to have from five to ten fluid bowel movements per day. During this time, she received therapeutic doses of vitamins and iron. The jaundice gradually faded.

On August 13, the patient was readmitted to the Hospital because of inanition and symptoms of multiple vitamin and calcium deficiencies. She had continued to lose weight; from her normal of 115 pounds, her weight was now down to 88 pounds. Physical examination revealed a chronically ill female who was minimally jaundiced. Her tongue was smooth and red. There was a pressure ulcer of the heel of the right foot. The abdominal wounds were healed save for a small sinus at the site of drainage in the cholecystectomy scar. The Trousseau sign was positive. Laboratory examinations showed that the serum calcium was 7.8 mgm. per 100 cc.; an oral glucose tolerance test revealed a flat curve; and the stool contained a large amount of fatty acids. A gastrointestinal series showed barium in the colon fifteen minutes after oral ingestion.

A low fat diet was prescribed, and the patient was given 45 cc. of kapectate and 10 drops of tincture of opium four times daily, plus vitamins, calcium chloride, and iron. Cortisone was added to this regimen and, while hospitalized, she gained four pounds. She was discharged on September 29, 1955.

Since September, 1955, her condition has gradually improved. The bowel movements have decreased in number per day, and her appetite and strength have increased. During the summer of 1956, her weight increased to 94 pounds, at which level it has been maintained. At the present time, she is having two or three formed stools per day. A regimen of cortisone, vitamins, and supplementary potassium is carefully followed.

COMMENT

This patient presented the classical history, signs, and symptoms of mesenteric arterial embolus. She was operated upon within one hour after admission to the Hospital, and it is probable that prompt surgical intervention, before shock supervened, was responsible, in large part, for the successful outcome.

The jaundice which this patient developed in the postoperative period was never adequately explained. When cholecystitis developed, it was assumed that the jaundice was caused by a common duct stone. This theory, however, was

disproved at exploration. Acute cholecystitis has frequently been reported as a complication of unrelated surgery. This case was apparently one of bacterial cholecystitis; culture of the bile revealed *B. coli*, and there were no stones in either the gall bladder or the common duct.

Postoperatively, the patient manifested the sequelae of massive intestinal resection. These included diarrhea, vitamin and calcium deficiencies, anemia, and weight loss. The metabolic aspects of this case have been studied intensively and have been reported by Kogan, et al. (2).

SUMMARY

1. A case of massive intestinal resection following superior mesenteric artery embolus has been presented.

2. Postoperative care following a massive intestinal resection has been discussed.

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PATHOLOGIC ANATOMY AT THE END OF THE EIGHTEENTH CENTURY

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A description and evaluation of the state of morbid anatomy at the end of the eighteenth century can only be meaningful if it is founded upon the history of its evolution. While in its slow progress pathologic anatomy gained purpose and inspiration from its correlation with clinical medicine, it is obvious that it primarily depended upon the study and knowledge of the structure of the human body. It seems, therefore, appropriate to survey briefly the early evolution of descriptive anatomy.

The archaic sources of the knowledge of the animal and human body were the kitchen and the cult (Sigerist) (1). Evidently such anatomical exercises were not inspired by scientific curiosity, but they might have sharpened the acuity of observation, as in ancient Babylonian hepatoscopy, and thus prepared the foundation for subsequent scientific inquiry.

The embalming of corpses which was practiced by the Egyptians for thousands of years did not provide an opportunity for exact observations because the methods, as described by Herodotus (2) (5th century, B. C.) and Diodorus (2) (1st century, B. C.), were too crude. It is true that the distinction of the internal organs by individual names, the condition primary for anatomy, was already known at the end of the Old Kingdom. But in embalming the corpses the organs were torn out through a small opening in the flank which made impossible the recognition of their mutual interconnection. The knowledge of the structure and function of the human body remained, therefore, highly speculative and the basic ideas proposed in Papyrus Ebers and Edwin Smith of a channel system, (Grapow) (3), originating in the heart and carrying air and liquids, such as blood, urine, tears, sperm and solid matters, such as faeces, cannot be regarded even as an adumbration of later anatomy and physiology.

The beginnings of anatomic knowledge among the ancient Greeks are veiled by uncertainty because the original works have been lost and we depend entirely upon the references of later authors, chief among them Galen. A detailed chronicle of the anatomic information and its development is not germane to this discussion, but reference cannot be omitted as to the significance of anatomy to the practice of medicine.*

Already in the latter centuries of antiquity the question arose whether Hippocratic nosology could have reached its high development without systematic knowledge of anatomy, which is not well documented in the *Corpus Hippocraticum*. According to Galen (7), anatomy was part of the oral tradition

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* Those interested are referred to C. Singer's *Evolution of Anatomy* (4), R. von Toeplitz's *Geschichte der Anatomie* (5), and R. Fuch's *Geschichte der Heilkunde bei den Griechen* (6).

which was transmitted from generation to generation by physicians and, therefore, a written system of anatomical knowledge was not needed. But this explanation was found unsatisfactory and the question again arose in the eighteenth and nineteenth centuries and is still under discussion today. Haller and Gruner (8) in the eighteenth century opposed the belief that dissections of the human body were performed in Hippocratic times, while Littre (9), Hirsch (10) and Haeser (11) in the nineteenth century were assured of this practice.

Toeplitz (12), in the early years of the twentieth century maintains that "the anatomy of the Corpus Hippocraticum was based upon occasional observations at the bedside, partly upon hypothesis but not upon dissection of human cadavers." Kapferer (13), a recent translator of the Hippocratic collection, is just as certain that "the careful and exact descriptions of the ancients could only be accomplished through a most accurate technique of dissection." Sigerist (14) not only sides with those who expressed disbelief in the existence of systematic anatomic knowledge in antiquity, but is inclined to explain this lack by a fundamental indifference of Greek medicine to anatomic thinking. The domination of medical doctrine by the speculative humoral theory accounts for its anatomic character and not the awe of the dead human body. But Edelstein (15), in a profound study of the history of the autopsy in antiquity, points out that religious belief in a life after death might have prevented dissection of the human body in Hippocratic times, but that soon afterwards this tendency began to change. A relaxation of religious objection is manifest in the words of Socrates in Plato's (16) *Phaedo*: "Be of good cheer then, my dear Crito, and say that you are burying my body only, and *do with that whatever is usual and what you think best*. This unconcern of the philosopher obviously became more universal and less than one hundred years later human corpses were freely dissected in Alexandria with the full support of the Ptolemaic kings. With Herophilus and Erasistratus anatomy enters the system of medicine and even pathologic anatomic observations can be traced to their investigations. Thus Herophilus (17) described the laceration of the ligamentum teres in luxation of the femur and Erasistratus (17) a stony hard liver in association with ascites. While the anatomic orientation of Alexandrian medicine did not survive for a long time afterwards, the significance of anatomy for the advance of medicine was recognized in the Roman Empire. This is documented by the historical introduction of Celsus (18) in his *De Re Medica*. Here the arguments in favor and against human dissections are dispassionately discussed and Celsus concluded that "the opening of cadavers is necessary for the students, because they must know the position and order of the parts and these are better recognized in dead bodies than in a wounded man."* Public opinion seemed also to have been concerned with the importance of human anatomy for the advance of medicine. This is revealed by a quotation from Cicero (19): "We are not familiar with our bodies. We do not know the seat of the organs and what functions each of them has. Therefore

* *Incidere autem vivorum corpora et crudele, et supervacuum est; mortuorum discentibus necessarium. Nam positum et ordinem nosse debent, quae cadavera melius, quam virus et vulneratus homo representant.*

physicians, who were interested to know have opened them in order that those may be inspected."* But the sanction of dissection of the human did not persist and in the second century A. D. its practice was abandoned in the Roman Empire except in the eastern provinces. This situation is clearly indicated in the statements of Galen (20) (129-200 A. D.) who deplores that human anatomy can no more be learned except in Alexandria. He himself had studied there and had continued in his anatomic investigations which made him the most important anatomist, not only of his period, but for more than a thousand years to come. Galenic anatomy retained supreme authority from which Arabic and subsequently revitalized western medicine derived all its knowledge of the formation of the human body. This is the more remarkable since Galen did not dissect human cadavers but his information, recorded mainly in his *Anatomic Administrations*, was obtained almost exclusively from zootomy. But the fundamental importance of Galen as an anatomist is not limited to the accuracy of his descriptions. Among his contributions to the advance of medicine is the realization that symptoms of disease can and must be correlated with alterations of the fabric of the human body. This diagnostic principle is unequivocally expressed in his most important work on pathology, "*Les lieux affectées*" (21): "There are very few essential symptoms of disease which do not point to the affected part. Indeed, the alterations of function indicate only the affected part."† Posterity has mostly neglected this precise formulation of Galen's thoughts on morbid states in favor of his humoral theories. But his forgotten clinical-anatomic correlation was to become the cornerstone upon which pathologic anatomy was erected. It took, however, more than a thousand years until the climate of opinion became favorable again for the dissection of human cadavers. It is evident from legendary tradition and historical documents that during the thirteenth century the idea of sanctity of the human body, firmly adhered to by Mohammedans, was gradually subverted in the Christian world. Legend tells (Artelt) (22) that Emperor Frederic II had the stomachs of two of his subjects opened in order to ascertain whether digestion proceeds better after exercise or after rest. The frivolity of his sovereign might well have encouraged his chief physician, Martianus, to ask for an imperial decree which made possible dissection of human cadavers for teaching purposes. This is the oldest document (1238) which authorizes the performance of public "anatomes" on the bodies of executed criminals. The relaxation of the taboo of the dead human body is further evidenced by the custom of dismemberment of the bodies of crusaders of noble birth who had died abroad. The parts were boiled and the bones, freed from skin and flesh, were returned to Europe for burial. This practice was prohibited by Pope Boniface VIII at the end of the thirteenth century but the papal bull did not interdict the autopsy for educational purposes and certainly not for the ascertainment of the cause of death.

* *Corpora nostra non novimus; qui sint situs partium, quam vim quaeque pars habeat ignoramus. Itaque medici ipsi quorum intererat ea nosse, aperuerunt ut viderentur.*

† Il existe très-peu de signes propres des affections mêmes qui n'indiquent pas le lieu affecté. En effet, les lésions de la fonction indiquent seulement la partie affectée. (Daremborg's translation).

In fact, the first authentic record of the dissection of a human body for this purpose dates back to the year 1286 (23) and in 1302 the first forensic autopsy was performed in Bologna on the body of a certain Azzolino who had died under suspicious circumstances. Although only congestion of the viscera was found, the authorities were satisfied and discontinued further investigations. During the plague epidemic in Siena in the year 1348, Pope Clement VI, (1342-1352, Avignon), ordered post mortem examinations and several principalities in northern Italy followed his example (Artelt (22), Campbell (24)). One might well ask here, what these early practitioners of morbid anatomy expected to find by their investigation of the human body. If their medical rationale as followers of Galen was really concerned only with the faulty mixture of the humores in disease, as Sigerist (14) maintains, one can hardly understand their interest in the inspection and exploration of the solid parts of the body. But it seems to me that medical thinking of antiquity was not so devoid of anatomical reasoning as Sigerist believes. It is true that for Galen the ultimate reason of health and disease was the condition of the humores and temperaments,* but he was well aware of the significance of the internal organs in the framework of his speculative physiology (*De usu partium*) (26). He correlated morbid symptoms to alterations of organs and his books on the affected parts give clear evidence of his anatomical reasoning. Lesions of internal organs were, therefore, the proximate causes of disease symptoms in the Galenic system of medicine which governed the diagnostic considerations of physicians in these centuries in which pathologic anatomy began to develop. The motive for the performance of autopsies on diseased bodies was, therefore, fully provided by the tenets of Galenic medicine and pathologic anatomy could well expand simultaneously with descriptive anatomy of the human body. But both disciplines remained closely allied and those who dissected for the purpose of systematic anatomy did not neglect the observation and recording of the abnormal. This is attested by the fact that the central figure of Rembrandt's *Anatomy Lesson*, Dr. Tulp, was the author of *Observationes Medicae* (27) which included not only autopsy reports but also pictures of pathologic specimens, among them a stone within the ureter, hydrops of the Fallopian tube and the notorious polyp of the heart. It can be seen from the literature of that period that every great anatomist was keenly interested in pathologic anatomy and that he dissected not only the cadavers of executed criminals referred to him by the authorities for teaching purposes (*anatomia publica*), but that he was also engaged in the examinations of the bodies of those who had died of disease (*anatomia privata*). Thus Columbus (28), a contemporary of Vesalius, devoted one chapter of his book *De Re Anatomica* to unusual findings at autopsy,† and from the roster of illustrious names, among them Ignatius-Loyola, it is evident that he performed many clinical autopsies. Vesalius, convinced of the supreme importance of systematic anatomy for medicine (*totius medicae artis fundamentum*) treats pathological findings as briefly as

* *Verum Hippocrates praefatus, corpus hominis in se continet sanguinem, pituitam, bilem flavam et nigram, deinde ait: et propter haec dolet, et sanum est* (25).

† *De iis quae raro in anatomico reperiuntur.*

possible (Roth) (29) in his great anatomic work *De Fabrica*. But he was fully aware of the significance of morbid anatomy and its correlation with observations in the living. He inquired into the life history of the cadavers he dissected in order to clarify rare observations. He planned to publish his experiences in morbid anatomy but apparently these records were lost. He performed private autopsies from his student days on (China-root letter) (30)) and tradition has it that the reason for his pilgrimage to the Holy Land from which he did not return was the performance of an autopsy on the body of an apparently dead woman patient.

The great anatomist Bartolomeo Eustachio (1500-1574), known for the discovery of the tube carrying his name and of the adrenal glands (*glandulae renibus incumbentes*), expressed regret in his older years that he had not paid more attention to pathologic anatomy (31)

Many of the great physicians of the sixteenth and early seventeenth century interested in anatomical studies were ardent advocates of the value of pathologic anatomy for the advance of medicine. Johannes Schenck von Grafenberg (1530-1598) (32), a practising physician of Strasbourg, published his own extensive experiences and collected the pathologic-anatomic reports of preceding years in his seven books of rare medical observations (1597) which makes this folio an excellent source for earlier pathologic-anatomic contributions. Its value is increased by the addition of a classified index and by the incorporation of aphorisms of ancient and more recent authors to inspire interest in pathologic anatomy. He tried to impress upon his readers how much this era had profited from pathologic anatomy. He was representative of the Renaissance and opposed belief in authority, advising rather to trusting the senses and personal experience (*rerum omnium magistram*) than subtle reasoning.

Volcher Coiter (1534-1576) (33), physician of the city of Nuremberg, recommended to the civil authorities to facilitate necropsies and admonished his colleagues to perform such investigations. He was so enthusiastic for his avocation as pathologic anatomist that he resigned from his post in Nuremberg and joined the expedition to France of Count Palatine Johann Casimir hoping that in view of the opportunities for dissecting the victims of battle he might penetrate the mysteries of obscure disease.* Marcellus Donatus, (34) the personal physician of the Duke of Gonzaga at Mantua, published in 1613 a *Historia medica mirabilis* in which he pleaded for the performance of autopsies: *Cadavera esse secunda*. This exhortation includes the often-quoted argument that it is more useful to dissect the cadavers than to leave them to be devoured by the worms. Wilhelm Fabry von Hilden, called Fabricius Hildanus (1560-1634), physician of the city of Bern, extolled in his book *Von der Fuertrefflichkeit und Nutz der Anatomy* (35) the lessons physicians have learned from autopsies. Without going into detail he refers to anatomical findings in a great variety of maladies. He points to the great advances which have been made in Italy and France compared with Germany because of the practice of necropsies. Thomas Bartholin, the

* *Castrensis medicus factus est, ut corporum dissecandorum occasione abstrusorum morborum penetralia cognoscerit.* (Schenck von Grafenberg).

illustrious Danish anatomist, was engaged in pathologic anatomic investigations but his records were lost when his house was destroyed by fire. In a short book, *De Anatome practica ex cadaveribus morboris adornanda consilium* (36), he draws a contrast between the descriptive anatomist who, as natural philosopher, can limit himself to the mere exploration of normal structures, while the physician-anatomist must search deeper and turn his eyes and mind towards the abnormal states. He concludes with the sentence: "From the bodies of the sick useful information derives."* Similarly, Francis Bacon (37) had pleaded for the investigation of the bodies of those who died of disease; to practice comparative anatomy, as he called it, and closed his appeal with the words: "In the differences of the internal parts are often found the immediate causes of many diseases." If one adds the often-quoted remark of William Harvey that the autopsy of one phthisic will advance medical knowledge more than the dissection of ten normal cadavers, one must understand how much hope was placed in pathologic anatomy in the sixteenth and seventeenth centuries.

The opportunities for such investigations were not much hampered by public sentiment. Benevieni (38), part of whose medical records were published in 1507 by his brother after the author's death in 1502, reports that only once was his request for the performance of a post mortem examination refused by the family of the deceased. The same liberal attitude is indicated by the occasional remarks of Vesalius and Columbus that autopsy was performed at the request or in favor of relatives and friends. Prominent physicians, such as Wepfer in Schaffhausen, Murali in Zurich, and Bartholin in Copenhagen, were given the privilege by the municipal authorities of performing necropsies on the patients who had died in public hospitals. Bartholin in his practical anatomy gives a vivid picture of the methods by which autopsies can be obtained, the opportunities and difficulties the prosector meets, from which one can conclude that the situation did not differ very much from that which exists in present days. He mentions the possibility of inspecting the organs while embalming, of gaining insight into the body cavities through an existing surgical incision; he is not averse to using persuasion and even deception in obtaining one's end, but recommends caution and tact.

In the British colonies of North America the significance of pathologic anatomy for the comprehension of disease was also recognized and we are indebted to Krumbhaar (39) for a survey of the situation during the seventeenth century. Champlain, describing an epidemic of scurvy, mentions that several bodies were examined in order to discover the cause of this "very cruel malady." Again in 1606 Champlain spent the winter in Port Royal and he writes: "Our surgeon, des Champs de Hornfleur, a man expert in his art, opened some of the bodies, to see if he might better recognize the cause of the disease, than in those who had died in the previous years." Cotton Mather reports an autopsy on his own son, where congenital rectal atresia was found, also on his baby sister who had died of a respiratory disease. The body was opened because of a suspicion that the child had died of witchcraft. The surgeon, Dr. Rossiter, who performed the autopsy,

* *Ex morboris corporibus salutaria praecepta fluunt.*

found absence of rigor mortis, blueness of viscera without apparent cause, blood under the back of the arm, the gall bladder all broken and curdled and the gullet contracted. He thought that these conditions were preternatural and the child's nurse was accused of witchcraft. This autopsy report is reminiscent of that of the already mentioned first forensic necropsy performed at Bologna in 1302, but the verdict was just the reverse. It reflects the inexperience and prejudiced ignorance of the medical examiner in these years when intolerance and superstition swept the colonies of the eastern seaboard. But for the medical historian it reveals the low state of development pathologic anatomy had only reached in this period. Its purpose was to correlate the morbid symptoms preceding death with obvious alterations of internal organs; in other words, to establish the proximate cause of death. If it failed, the remote causes were searched for and speculation or superstition were used for explanation.*

Thus at the end of the seventeenth century pathologic anatomy was widely practiced in the western world and under conditions very favorable for its development. A great number of observations had been published, but they were scattered in medical and surgical textbooks, collections of interesting cases, periodicals or letters. It became desirable to collect them, to make them available to the interested student of medicine. Theophil Bonetus (1628-1689), a physician of Geneva, who had retired from practice because of a hearing defect, collected nearly three thousand cases and published them in 1679 as *Sepulchretum Sive Anatomia Practica* (41). The complete title indicates the scope of the work and the significance which Bonetus attributed to it. It reads in translation: "Repository or anatomy practised on corpses deceased of disease, which reports the histories and observations of all alterations of the human body and reveals the hidden causes. Indeed, it (anatomy) deserves to be called the foundation of real pathology and of proper treatment of disease, even the inspiration of old and recent medicine."† Obviously, today not even the most enthusiastic supporter of pathologic anatomy would concur with this baroque glorification. But even a century ago Bonet's monumental compilation was regarded only as a welcome source book for old observations, but not as a guide for future investigations and, therefore, the question can be raised for the reasons of the slow development of pathologic anatomy which, after two centuries, had not yet reached the road which would lead it to the summit in the nineteenth century when it truly became the foundation upon which rested medicine of this period, and from which it has not yet been dethroned. There are several obvious answers to this question. Anatomy of the normal human body had to be further developed, in order that the alterations found in the diseased body could be more clearly comprehended. The confusion of post mortem with intra-

* *Hinc magno cum labore et studio multa recuperat perscrutaturque sensuum ope, atque in ea primum incumbens, quae sensibus sunt obvia, occultiora tandem ratione colligit sola mente comprehensa.* (Fernel, *Physiologia*, Lib. I, p. 1) (40).

† *Sepulchretum sive anatomia practica ex cadaveribus denatis, proponens historias et observationes omnium humani corporis affectuum ipsorumque causas reconditas revelans. Quo nomine, tam pathologiae genuinae quam nosocomiae orthodoxae fundatrix, imo medicinae veteris ac novae promptuarium dici meretur.*

vital changes was a serious problem which retarded progress. For instance, the erroneous interpretation of post mortem cogula within the cavities of the heart and the lumen of large vessels as dangerous polypi continued almost for centuries although Kerekring had pointed out their true nature in 1673. Glisson, in his book on rhachitis (42), warned of premature conclusions in correlating morbid symptoms with organ lesions. He pointed out that many chronic diseases might be associated with other maladies. He demanded that the prosector carefully ascertain which lesions are always present, which frequently and which only rarely. In other words, he requested exactly controlled observations. But beyond these retarding factors inherent in the descriptive methodology of pathologic anatomy there was another more important reason which prevented the development along dynamic lines of later centuries. It has already been previously indicated that in the Galenic system of medicine organ alterations were considered as proximate causes of morbid symptoms but that the ultimate reason was hidden from the *manus oculatae* (Fernel, Bonet), the seeing hands of the morbid anatomist. Jean Fernel, the great French physician and pathologist of the sixteenth century, might have sensed this intrinsic inadequacy. Sir Charles Sherrington (43) formulated this feeling with these words: "Running through all (i.e., his contemplations) is an implication that the body is the scene of processes which, could our senses get at them, would supply medicine with its long-needed clues. And John Locke, in a fragmentary paper on anatomy which has been unveiled by Sir William Osler (44), expresses his misgivings about the value of pathologic anatomy quite clearly: "That nature performs all her operations in the body by parts so minute and insensible that I think nobody will ever hope or pretend even by the assistance of glasses or other inventions to come to a sight of them." From the gross parts he thinks not much can be learned. "We see not the tools and contrivances by which nature works. Though we cut into the inside, we see but the outside of things and make but a new superficies for ourselves to stare at." These words are quite in line with "his three-termed relation between the sensed and the scientifically objective factors in nature," (Northrop) (45). Locke's basic objections were apparently shared by his friend Thomas Sydenham who was also skeptical of the value of anatomical investigations for the comprehension of disease. The erroneous Galenic concept of the functions of the organs and their dependence on the speculative humores and temperaments made a rational correlation of clinical symptoms and morbid findings at autopsy almost impossible. This is well shown by many case reports of that period such as the anatomical relation presented by Tornius and translated by Lynn Thorndike (46). Tornius, a Florentine physician of the late fifteenth century, described the autopsy of a child who had died of a disease "not fully understood by physicians." The autopsy description leaves no doubt of the presence of multiple liver abscesses, most probably of a pylephlebitis of the portal vein and possibly of a pulmonary artery embolus or thrombosis. In his analysis Tornius first explains the clinical symptoms according to the doctrines of Galen and Avicenna and his foregone conclusions are then flimsily corroborated by the autopsy findings. Similar reasoning is encountered in some reports

of Benevieni. Even as late as 1661, Bartholin (47) explains perforated ulcers of the ileum as the result of an inflammation produced by an overflow of sharp and corrupted biliary humores. The only reasonable correlations are found in such case reports in which the clinical symptoms were simple and unequivocal, such as case 34 of Benevieni (38) of a nun in whom he found "the intestines contracted by a thick callus so that only a narrow channel was left and the excrement could scarcely pass through." He closes the analysis with the statement: "This, however, I had suspected even in her lifetime, seeing that she had struggled against something hard that pressed on her bowel." It is interesting that the only clinico-pathologic report of John Locke (48) is also concerned with an obstructive lesion, this time of the right ureter causing pyonephrosis, apparently the result of an adhesive pelveo-peritonitis. There are many other cases reported by Bonetus in which mechanical factors determined the leading clinical symptoms, such as Fernel's case which has been interpreted in modern times as the first report of a perforating appendicitis, instances of incarcerated inguinal hernias, carcinoma of the esophagus or pylorus. But whenever the situation was more complicated humoral speculations were invoked for explanation, or a correlation was omitted. This is well illustrated by the report on the autopsy of Emperor Maximilian II in 1576 (49).

This haphazard attitude toward pathologic anatomy seems to me to be in line with the dominant philosophical ideas of the period. The positive correlations on mechanical grounds supported Descartes' concept of man as a machine and proved the value of autopsies. The equivocal observations, however, were not insignificant either because they served the purpose of Bacon's thesis of empiricism as the foundation of natural science. But pathologic anatomy as a force for the rationalization of medicine had to contend with the still prevailing humoral doctrine, even when amended by chemical theories. But with the discoveries in physiology, initiated in 1628 by William Harvey which made the seventeenth century so important a period for the advance of medicine, clinical symptoms could be better integrated with pathologic anatomic findings. This is well illustrated by the report of the terminal illness of Johann Jakob Wepfer and of his necropsy. Wepfer (1620-1695) great as a physician, pathologic anatomist and experimental toxicologist, suffered in his old age from dyspnea, orthopnea, slow, occasionally irregular pulse, precordial pain, edema and coldness of his extremities, evidently the symptoms of cardiac insufficiency. He requested that his body should be examined after death and his son-in-law, the famous Conrad Brunner, published a detailed medical history (50), necropsy findings and a clinico-pathologic correlation. The autopsy disclosed ascites, bilateral hydrothorax, edema of extremities, hypertrophy of the heart and arteriosclerosis of the aorta and peripheral vessels, of which a drawing is added to the report, the first illustration of arteriosclerosis in the medical literature. Brunner, correlating the clinical symptoms with the pathologic anatomic findings, stresses the embarrassment of the greater and lesser circulation, he explains the hydrops as the result of stasis according to Lower's experiments showing that ligation of the vena cava causes ascites. He mentions that this mode of death is frequent in old

people and refers to two cases of his own experience with similar clinical and anatomic findings. This observation is certainly not startling in present days but it was of utmost importance at the end of the seventeenth century and represents a break with former pathophysiologic considerations. This is demonstrated by the added remarks of Brunner: "Those who adhered to the beliefs of the ancient writers would have attributed death to the loss of vital heat. But just in our case the error of such a concept is evident; it is the blood, indeed, which is responsible for natural heat. If deprived of its circulation, the external parts become cold and this was a symptom of which Wepfer complained so frequently."

With the beginning of the eighteenth century, the scope of pathologic anatomy in its relation to clinical medicine did not change but its range became better defined. The observations at autopsy grew more exact, the descriptions more complete, the correlation between observations in the living and anatomical findings broader. This can well be seen in the work of Lancisi, Ramazzini, and Boerhaave. In studying Lancisi's (1654-1720) book, *De Subitaneis Mortibus* (51), published in 1707 reporting on his investigations of cases of unexpected death among the population of Rome, one finds detailed clinical and anatomical descriptions, in which every attempt is made to establish reciprocal relations between them. In the presentation of the case of a 60 year old man, for instance, in whom he found an abscess of the right frontal lobe, he refers to a cystic tumor in the posterior part of the liver adherent to the diaphragm and filled with rusty colored, clay-like material. This was most probably an old *echinococcus* cyst with inspissated contents. The patient had suffered for a long time from a dry cough and Lancisi proposes that the diaphragmatic adhesion might have been responsible. I believe it is immaterial whether his interpretation was correct. The case is quoted only to illustrate the accuracy of his observations and the trend for clinico-anatomic correlation. The precision of his observation* and the abundance of available clinical and autopsy material made him the celebrated author of a treatise on aneurysms (52) in which he tried to account for the evolution of the arterial dilatation. He gives a description of four layers of which the wall of the aorta and arteries consists. He shows how injury to the outer layer weakens the wall which cannot properly resist the impact of the blood. Such injuries were not uncommon in a period when venesection was most common and performed by unskilled barber surgeons. But when he comes to the consideration of aneurysms in syphilitics with which he was well acquainted, he does not hesitate to invoke acrid and corrosive humores for the evolution. This and similar discussions in his two major works indicate how much Lancisi was still dominated by humoral speculations under the disguise of iatrochemical theories. He was equally ready to apply the system of the iatromechanics and to explain morbid phenomena and death as the result of changes in the tension of the fundamental fibers of the organism. In his inconsistency he was a true child of the seventeenth century which "was able to believe without any effort or striving that 'truth' was not all of one order" (Willey) (53) Bernardino Ramazzini's (1633-1717) great contribution was the recognition of a correlation between

* He gave, for instance, exact measurements in his descriptions.

occupation and disease. While Diemerbroeck (54) in the preceding century was probably the first who described the indurated lungs of stone-cutters, it was Ramazzini who fully established the relationship in his book, *De Morbis Artificum* (55)

Bedside teaching, originally developed in Padua, was brought to Leyden by Johann Heurnius and further promoted by his son, Otto. But it reached eminence under Hermann Boerhaave, the great European clinician of the first half of the eighteenth century. In contrast to Thomas Sydenham, whom he greatly admired, he was convinced of the importance of post mortem examinations which the students had to attend. His pupil, Van Swieten, transplanted his educational principles to Vienna where under one of his successors, Johann Peter Frank, the performance of autopsies was made compulsory in public hospitals and facilitated by the appointment of a salaried prosecutor (Aloys Vetter). In this way Boerhaave furnished the most powerful stimulus to the advancement of pathologic anatomy in the eighteenth century, although his personal contributions to the literature of the subject were not significant. Yet his concise formulation as to the usefulness of necropsies for medicine deserves comment. In the introduction to his "*Atrocis, Rarissimique Morbi Historia Altera*" (56), (an enormous mediastinal neoplasm, possibly lymphosarcoma), he states the purpose of his publication: "That in spite of most detailed description of all disease phenomena one does not know anything of the cause until one has opened the body." He continues, that he will try to give a picture, as accurate as possible, of his observation in order that in a subsequent case of the same nature, the correct diagnosis might be reached. And he closes with the hope that the discernment of the experienced physician may once succeed in recognizing the disease in its early beginnings, when it still can be eradicated. Boerhaave's approach to the problem of diagnosis in the living with the help of pathologic anatomy is that of anticipation based upon statistical congruence of symptoms and anatomical findings. Leopold Auenbrugger (57) tried to elicit new perceptible diagnostic signs which were determined by the anatomical alteration in each individual case. He became the creator of a direct clinico-anatomic correlation, which was continued by Laennec and found its culmination in the application of Roentgen's discovery making visible the hidden changes of organs. Nearly a century had passed since Bonetus had assembled in his *Sepulchretum* the available pathologic anatomic observations together with the correlated clinical data which had been reported in the past centuries. The second edition, published by Manget in 1700 with some additions, was hardly an improvement over the first although Manget maintained in the preface that he had rearranged the index in order to facilitate its use as a guide for diagnosis. The time was ripe for collection of the new observations and critical review of the old ones. This work demanded broad personal experience in pathologic anatomy and clinical medicine, critique and the courage of conviction in the supreme value of the method of clinico-anatomic correlation for the advancement of medicine.

In 1761 Giovanni Battista Morgagni (1682-1771) published his monumental book *De Sedibus et Causis Morborum per Anatomen Indagatis*. (58) He brought

to his task the practical experience of 60 years as professor of anatomy and medicine at Padua, a persevering, almost perfectionist devotion, well manifested in his previously published *Adversaria Anatomica* and an open, yet highly critical mind toward the acceptance of his own or others' observations. He had at his disposal the notes and comments of his teacher and friend Valsalva and personal communications from contemporary authors with whom he was friendly, such as Lancisi and Ramazzini. His efforts were facilitated by the preceding compilation of Bonetus. It would be impossible to survey the factual knowledge contained within his five books which cover the manifestations of disease from the head to the heel (*A Capite ad Calcem*). But attention must be called to the two appended indices which list the clinical data with the correlated anatomical findings, and anatomical observations with the corresponding clinical symptoms. Morgagni's great work gave strength to and confidence in the reliability of the perceived facts established by pathologic anatomic investigation and in the importance of their correlation with observations at the bedside. The first assertion seems well illustrated by the response of Samuel Johnson to Boswell's question whether he believed the tale that the scorpion, if surrounded by a ring of fire, withdrew to the center and committed suicide by piercing its heart with its caudal sting. Johnson was not quite sure, but he would accept this story if an autopsy had been performed by Dr. Morgagni. But more importantly, the second affirmation made Morgagni's book and principles the beaconlight which guided the progress of medicine for nearly a century. The recognition by Fothergill and Jenner that coronary sclerosis is associated with Heberden's clinical syndrome of angina pectoris followed still within the century. But the first half of the nineteenth century was to reap the fruits of Morgagni's effort in the disclosures of the great French clinician-anatomists, such as Bayle, Laennec, Louis and others, of the British school headed by Bright, Hodgkin and Addison, and of Rokitsansky, Skoda and Hebra in Vienna. Their discoveries have shown that the puzzling variability of clinical manifestations of disease becomes clarified by the unity of the seat of the anatomic alterations. But was the cause also revealed, as Morgagni maintained in the title of his book? Pathology of today can no more accept this thesis and the decline of esteem pathologic anatomy has suffered in the past decades is due to the dissatisfaction with this simplification. In fact, the progress of medicine would have been arrested had later generations limited themselves to the causality of Morgagni. But in fairness to him, one must try to understand his idea in the framework of opinion of his period.

It has been repeatedly stated before that the early practitioners of pathologic anatomy recognized that they could reveal only the proximate causes of disease but that the remote reasons must be searched for by other methods. This point of view is amply manifest in their writings and Fernel clearly expressed it in the already quoted sentence, that while one can ascertain the obvious causes with the senses, the hidden causes can be comprehended only by the mind. But the mind of physicians of these times had indulged in fruitless speculations; their hopeless inadequacy was fully recognized in the eighteenth century. Molière had castigated them even before. Can one not understand that the sober, almost

pedantic mind of Morgagni saw salvation in simplification, in reliance only on the clearly perceptible facts of anatomy? And he had support for this principle in the contemporary philosophy of David Hume who believed that the idea of causality originated in the constant association of sense perceptions, which were for him the only acceptable evidences of reality. Did not this concept justify Morgagni's search for correlation and possibly the hope to find the causes of disease by never-ceasing attempts to correlate the sensual perceptions of the clinician with those of the anatomist? But Hume's concept of causality was superseded by Kant's postulate of aprioristic (extrasensual) forms of cognition which organize the observational material provided by the senses, and one of these aprioristic categories of the reasoning mind was causality. But the mind, as Kant conceived it, could neither indulge in unproven speculation nor be satisfied with the facts hitherto perceived. It had to search deeper and this urge led to the alignment of medicine with the aspiring fundamental sciences and to experimental physiology and pathology. The eighteenth century pathologic anatomists, with the possible exception of John Hunter and Matthew Baillie, did not recognize the necessary change in direction towards a comprehension of the morbid process. How pathologic anatomy of Morgagni under the leadership of Virchow adopted the new role of the mind in Fernel's sense is the story of the nineteenth century which still powerfully influences our endeavors in morbid anatomy today.

I should like to conclude my presentation with a question. Is there any merit in such historical studies, do we learn anything by unearthing facts which have been antiquated and replaced by modern investigations? I have no hesitation to answer this question in the affirmative. The historian looking backwards learns from his studies that pathologic anatomy and, for that matter, medicine as a whole could develop only in the climate of reason of its period, to use the words of Ecclesiastes: "To everything there is a time and a time to every purpose under the heaven."

He begins to comprehend the workings of the mind of our predecessors. And looking forwards, he notices that most of these trends are still in operation, may be unconscious to those who are spurred by them in their investigations. And while historical studies and contemplations do not contribute useful factual information, they might be helpful for the education of the mind.

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PROFILE FEATURES OF BENIGN GASTRIC NICHES ON ROENTGEN EXAMINATION

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The most characteristic feature of a benign gastric ulcer on roentgen examination is the presence of a conical or collar-button shaped projection from the lumen of the stomach, the well known Haudek niche. Recognition of a niche requires that tangential observations must be made, that is, profile views obtained. It has been known for some time, however, that a perfectly classical ulcer niche, no matter what its size, may turn out to be malignant (1, 2). There are, however, additional features which may be seen in association with a niche which are of assistance in differentiating benign from malignant ulcer craters. A sign of considerable importance has recently been described by Hampton and his coworkers (3) which, when seen, appears to be distinctive of benign ulceration. The "Hampton sign" consists of a thin, lucent line with parallel straight margins which traverses the orifice of the niche. It is about 1 mm. in width and often appears as if drawn by a pencil (Figs. 1, 2). The width of this line appears to be essentially independent of the size of the crater. Reconstructions of gross specimens in plastic by these authors indicate that this lucent line represents the undermined mucosal edge, or ledge, surrounding the ulcer crater. It therefore also represents the demarcation between the ulcerated area and the general lumen of the stomach. Since the undermined mucosal edge is extremely thin it is necessary that it be brought into profile in order that it may be demonstrated. For the same reason, radiographic exposure must be optimum if the small differences in density are to be satisfactorily recorded. The line cannot be seen on fluoroscopic examination. Compression is not an important factor in demonstrating this sign except insofar as it may assist in bringing the niche into view by displacing adjacent portions of the stomach. Occasionally, a double line may be seen (Fig. 3A) presumably when the crater is projected not quite tangentially, that is, portions of both the anterior and posterior margins are visualized. Under these circumstances, a line of increased density may be noted between the two lucent lines and, in fact, this line of increased density may be more obvious than its lucent borders. The complete length of the Hampton line may not be demonstrated. Moreover, the line may not be seen as such but small distinct notches may be seen at the superior or inferior margins of the orifice of the crater (Figs. 2, 3A, 4A) and appear to result from the same cause and have the same significance as the line itself.

Unfortunately, the Hampton line is seen in a relatively small number of benign gastric ulcer niches. It is more common, to see a lucent band intervening between

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FIG. 1A. Small benign ulcer high on the lesser curvature. Spot film shows a niche with a sharply drawn thin lucent line crossing its neck at its opening into the stomach. This is a "Hampton sign". Between the lucent line and the general lumen of the stomach, there is a somewhat triangular or funnel-shaped collar produced by a lack of complete distensibility due to thickening of the gastric wall immediately surrounding the ulcer crater.

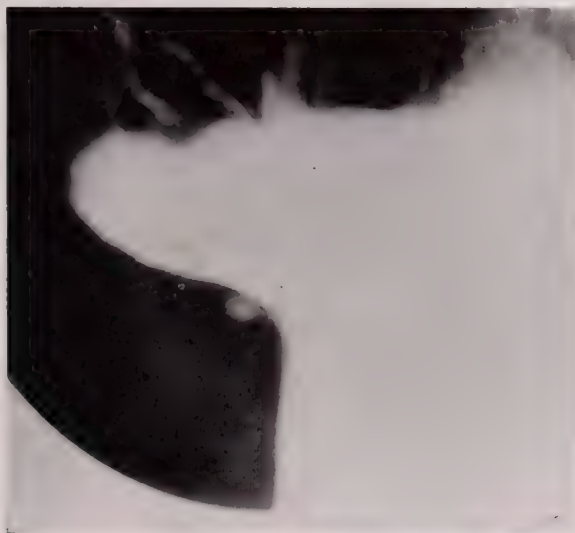


FIG. 1B. Same examination as Fig. 1A in a slightly different projection, presumably with less compression, the lucent line coincides with the contour of the filled stomach.

the niche and the general lumen of the stomach (Figs. 3B, 4, 5). We have referred to this as an "ulcer collar". It has been suggested that this lucent band is simply a projection of the Hampton line when it is not projected tangentially (3). This, however, does not appear to be true since both the Hampton line and an ulcer collar may be seen in the same case (Figs. 5B, C, D). The ulcer collar is a mani-



FIG. 2. Large benign ulcer on the posterior wall of the body of the stomach near the greater curvature. With the patient prone, the stomach was markedly horizontal in position. Between the crater and the lumen of the stomach, there is a thin lucent line, that is, a "Hampton sign" is present. This line is best seen proximally where it appears in profile as a rather deep notch. The depth of this notch depends on the degree of undermining. The adjacent gastric wall, over a considerable distance around the ulcer, shows marked limitation in distensibility. This creates the appearance of "an ulcer mound" with the crater located in its center. The contours of the mound join the normally distensible stomach at an obtuse angle without any sharp break in continuity. The surface of the mound is smooth with a double contour in places due to overlying intact folds.

festation of limited distensibility of the gastric wall immediately surrounding the niche. This limitation of distensibility may be the result of inflammatory exudate about the crater with perhaps some resulting local spastic contribution. This limited distensibility, in effect, produces a persistent marginal fold which may intervene between the crater and the adjacent radiating fold pattern (Fig. 6). The width of this collar is to some degree a function of the degree of compression because, as compression is increased, the extensions onto the adjacent gastric walls may be visualized (Fig. 5). The width of the collar is roughly proportional to the size of the ulcer crater. Since this collar is considerably wider than the Hampton line, it is not necessary to bring the niche into exact profile in order that it may be seen (Figs. 4, 7). The degree of inrolling of the wall of the stomach over the entrance to the crater is variable so that the length of the collar may be greater or less than the length of the niche itself. The margins of the collar often flare out slightly as they join the contour of the lumen of the stomach but they may be straight or indented. These margins have a consistent configuration during the course of a single examination provided the region is



FIG. 3A. Benign ulcer on the lesser curvature below the cardia. Spot film shows two vertical parallel lucent lines at the neck of the crater. Between the two lucent lines, there is a vertical opaque line which in some cases is the more obvious feature. The convex indentation on the inferior aspect of the neck of the crater which extends onto the adjacent gastric wall producing a scroll-like appearance is the result of thickening of the gastric wall about the ulcer crater. (The row of metallic sutures is due to a previous cholecystectomy.)

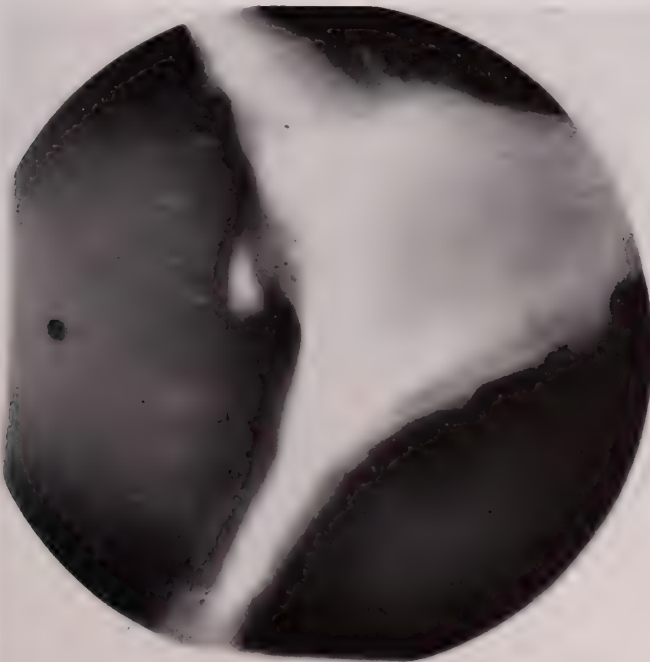


FIG. 3B. Same examination. With compression, a lucent collar is seen between the crater and the lumen of the stomach. A Hampton line is not seen but the sharp straight demarcation of the barium in the ulcer crater from the lucent collar may represent the outer border of such a line. Under these circumstances, the inner border would not be seen since its lucency fuses with the remainder of the collar. The scroll-like configuration of the inferior border of the collar is again evident. The upper margin of the collar is straight. The collar is homogeneous and is not sharply demarcated on its luminal aspect.



FIG. 4A. Benign ulcer of the lesser curvature of the stomach. A large niche with a broad ulcer collar. A small but distinct notch is seen inferiorly at the junction of the crater and the collar. A notch such as this has the same significance as the Hampton line.

completely filled but they may vary somewhat in exact appearance depending on the degree of compression, i.e. the appearance does not suggest complete rigidity. In small niches, the width of the collar may be quite small (Fig. 8) and, in such cases, differentiation from the Hampton line may be questionable. This is, however, likely to be of little importance since the significance is similar.

The ulcer collar noted above has been described as a homogeneous gray or lucent band intervening between the crater and the general gastric lumen. The relative lucency of this collar as compared to the density of the barium in the crater and the barium in the general lumen of the stomach may be evident only



FIG. 4B. Benign ulcer niche with a collar, located high on the posterior wall of the greater curvature.

with compression. However, this is not necessary in all instances (Figs. 4A, 4B). The lucency produced by compression indicates that the collar is less resistant or more pliable than the ulcer crater itself. In those instances where the lucency is present without compression and in which the length of the collar is greater than the length of the crater, it is necessary to assume that the marginal fold (or folds) creating the collar is not symmetrical (Fig. 9). In its most common location along the lesser curvature, this would indicate that the thickness of the fold producing the collar is greater in front and in back than it is above and below. The asymmetry of the collar may represent a residual manifestation of the normal, more or less longitudinal or vertical, course of the gastric folds.

The lack of distensibility or the induration of the gastric wall immediately about a benign ulcer crater which produces a marginal fold and an ulcer collar

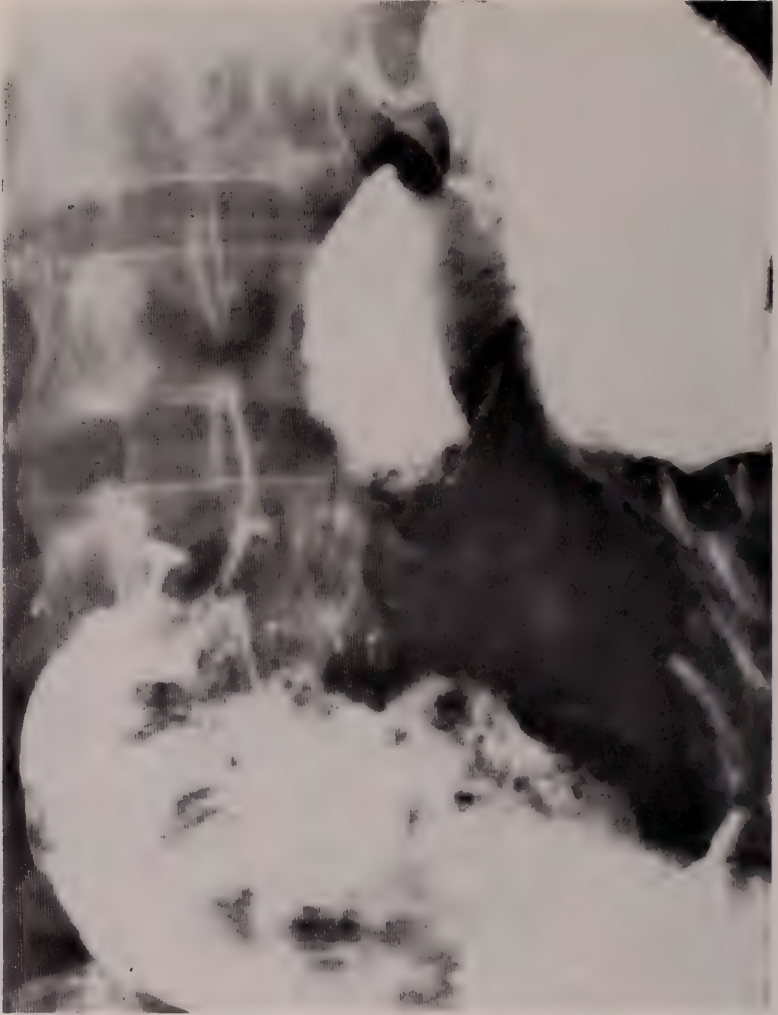


FIG. 4C. A giant benign ulcer of the posterior wall near the lesser curvature which shows a large collar between the crater and the general lumen of the stomach.

may extend for a considerable distance beyond the crater in all directions. This extension will then produce a rather considerable area about the crater of limited distensibility which manifests itself as an "ulcer mound" (Fig. 10). An ulcer mound of this type may be seen with small niches (Fig. 8) or with large (Fig. 2). When the mound is marked, the niche does not project beyond the contours of the normally distensible stomach. However, the niche-like characteristic is still evident by the projection into the center of the mound. The surface of such a mound is sharply demarcated and smooth with intact folds over it and in most instances the margins of the mound join the adjacent margins of the stomach in a smooth flowing fashion without any sharp discontinuity. Occasionally, however, a rather abrupt transition will create the impression of a sharply demar-

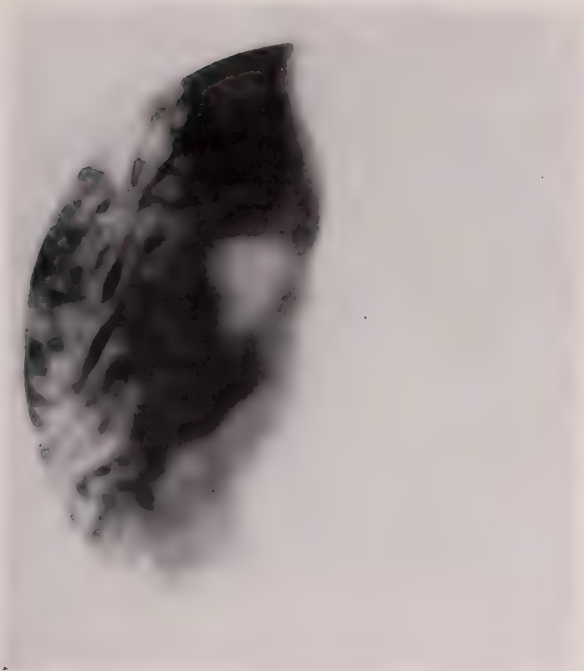


FIG. 5A. A benign gastric ulcer on the lesser curvature immediately above the reentrant angle. Barium filling the crater is sharply demarcated on its luminal aspect. A lucent band or collar is interposed between the crater and the main gastric lumen. This collar is continuous with a rather flat ulcer mound which surrounds the crater in symmetrical fashion.



FIG. 5B. Re-examination 16 days later shows marked diminution in the size of the crater with disappearance of the ulcer mound. A very shallow collar is present. In addition, however, between the collar and the crater, a Hampton line is seen.



FIG. 5C. With moderate compression, the ulcer collar appears somewhat wider.



FIG. 5D. With greater compression, the lucency of the collar is increased and extends onto the adjacent gastric wall where the ends of thick radiating folds can be made out.

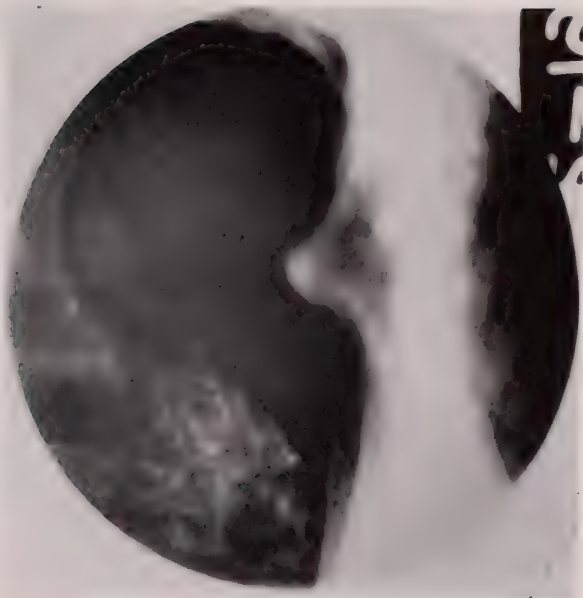


FIG. 6A. Benign ulcer high on the lesser curvature of the stomach. A spot film with compression shows thick folds radiating towards the crater but fusing with a circular fold at the neck of the crater. As a result, the barium-filled sulci between the thick folds do not extend into the crater but stop a short distance from it.



FIG. 6B. Re-examination four months later shows persistent radiating folds with no ulcer crater or ulcer collar. The involved area shows slight diffuse limitation of distensibility.



FIG. 6C. Eight months after the original examination, there is recurrence of a small ulcer crater. No Hampton line and no ulcer collar are demonstrable.



FIG. 7. Benign ulcer at reentrant angle in "semi-profile" projection. The lucent ulcer collar appears to be part of the longitudinal fold pattern and in this sense may be referred to as a marginal fold. However, it is also necessary to visualize a circumferential or circular component to the fold producing the ulcer collar in order to explain the presence of its superior and inferior horizontal borders.



FIG. 8. Small benign ulcer high on the lesser curvature of the stomach. A thin, somewhat curved lucent line is interposed between the crater and the general gastric lumen. Differentiation between a Hampton line and a shallow ulcer collar is difficult but presumably of no great importance since the significance is similar. A typical ulcer mound is also present.

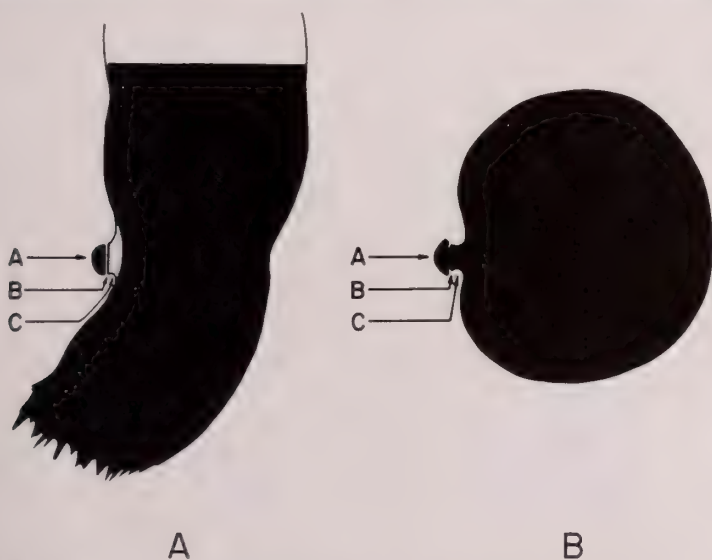


FIG. 9. A. Diagrammatic representation of a benign ulcer niche along the lesser curvature. The stomach has been filled with barium (shown in black). The crater per se, in black, is indicated by A. B represents a Hampton line. Between this line and the general lumen of the stomach is a gray, homogeneous collar (C) which produces a tubular or somewhat triangular communication between the crater and the main gastric cavity. The presence of this collar indicates that the transition between the crater and the stomach lumen is not abrupt but through a short somewhat funnel-shaped tunnel which is lined by incompletely distensible gastric wall. The mucosa lining this tunnel is intact but a so-called "mucosal pattern" is not seen because the collar consists essentially of a thick fold which gradually flattens out as it joins the normally distensible stomach contour.

B. Diagrammatic cross section of the filled stomach at the level of the ulcer niche. The lucency of the collar in the "A-P" projection is explained by anterior and posterior indentations on the "tunnel" by marginal folds (C) which make up the collar. The indentations on the superior and inferior margins of the collar (C in figure 9A) are less marked. B indicates the undermined mucosal ledge of tissue which produces the Hampton line. A is the true crater.

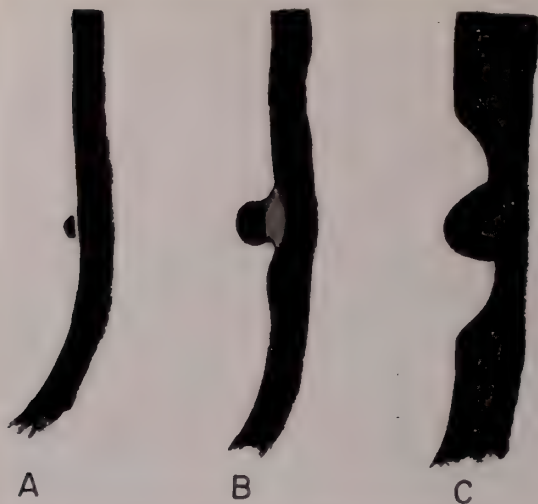


FIG. 10. A. Small niche with Hampton line only. There is an abrupt transition between the crater and the general gastric lumen.

B. A larger niche plus an ulcer collar, that is, the transition between the crater and the general gastric lumen is not abrupt but via a short transitional funnel-shaped tunnel produced by a marginal gastric fold of limited distensibility.

C. An ulcer crater in the center of an ulcer mound. In contrast to a flat carcinoma with elevated edges, the mound represents a smooth hemispherical protrusion which is interrupted by a central ulceration. The "shoulders" of the mound adjacent to the central ulcer may, however, simulate the edges of an ulcerated carcinoma. Differential features which may be useful are the single, smooth, contour of the mound and the obtuse, somewhat pliable angle at its junction with the normally distensible gastric wall.

cated smooth filling defect with an ulceration in its center. Differential diagnosis from an ulcerated intramural tumor such as a myoma may then be quite difficult. In projections which are "en-face", a marked ulcer mound may produce a "halo" surrounding a crater (Fig. 11). Under these circumstances, it is necessary to distinguish the defect surrounding the crater from the elevated ridge of tumor tissue seen in the type of ulcerated carcinoma described by Carman (1) and by Kirklin (4). This differentiation may be quite uncertain unless the features of the "meniscus complex" are unequivocal (Fig. 12). During healing under medical therapy, however, a flat ulceration with no features typical of a benign ulcer, that is, without a Hampton line and without an ulcer collar, may decrease in size and present itself as a niche with typical findings. The difficulties involved in differentiating a halo about a flat benign ulcer crater from the marginal ridge of an ulcerated carcinoma are evident by comparison of Figures 11 and 13. Occasionally, pliability of the mound is obvious during filling and excludes a carcinomatous ridge (Fig. 14).

A niche with characteristic features as described above is rarely seen in the antrum of the stomach. In many instances, this may be the result of marked spasm of the antrum so that local features around the crater are obscured by inability to distend the antrum as a whole. Even in instances where lack of distensibility is confined to the region about a crater in the antrum (Fig. 15),

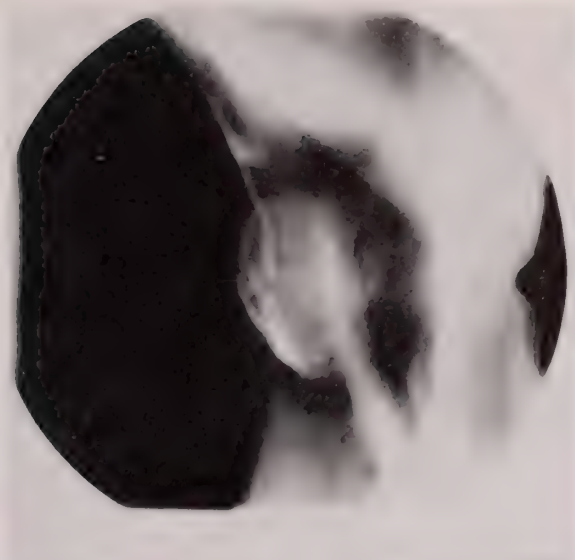


FIG. 11A. Benign ulcer (proved at operation) high on the posterior wall of the stomach. In this view, the crater is projected almost "en face". There is a wide halo around the crater which is not sharply demarcated along its outer contour. There are no discrete nodular excrescences superimposed on the halo.

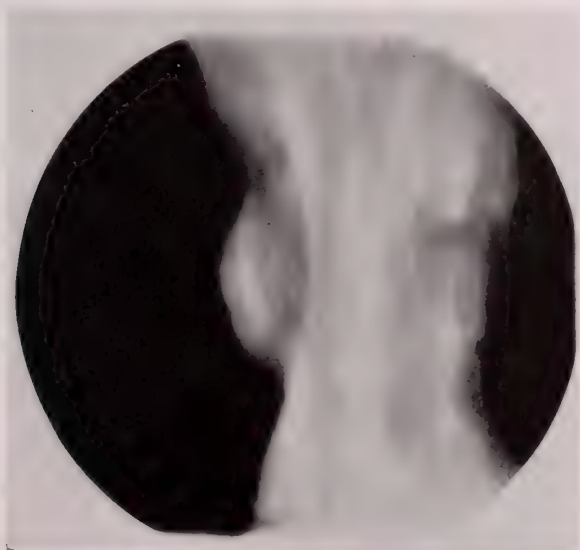


FIG. 11B. Same examination; a profile view. The ulceration is flat and projects slightly beyond the contour of the filled stomach. There is no Hampton line and no ulcer collar. There appears to be, however, a rather thick smooth curved marginal fold which reaches the contour above and below the ulcer crater and produces slight indentations at these sites.



FIG. 12. A flat ulcerated carcinoma of the lesser curvature aspect of the body of the stomach with features typical of the Carman-Kirklin meniscus complex. A somewhat irregular, elongated, ulcerated area is seen which 1) does not project beyond the gastric lumen, 2) is surrounded by a curved ridge with nodular thickenings which indent the ulcerated area and 3) retains barium.

the appearance of a mound with an ulceration at its summit is rarely demonstrable. Unfortunately, a complete arcuate ridge may be seen surrounding such a crater simulating the "meniscus complex". One of the difficulties in studying the antrum is the fact that lesions on the anterior or posterior walls cannot be brought into satisfactory profile projections because the filled stomach proximal to the antrum and the duodenal bulb distal to the antrum serve to obscure these walls in the oblique and lateral projections.

Experience to date indicates that a typical Hampton line is practically pathognomonic of a benign ulcer. We have seen one instance in which barium apparently collected between thick folds along the greater curvature and, on a single spot film, the impression of a Hampton line was given (Fig. 16). A Hampton line has



FIG. 13A. Partial "en face" view of an ulcerating carcinoma. A large circular ulceration is present with a halo about it. In places, for example superiorly, the halo is rather sharply demarcated along its outer contour with normal folds terminating abruptly at this margin. The border of the crater is somewhat irregular as compared with the crater demonstrated in Figure 11A.



FIG. 13B. "Profile view" fails to demonstrate any projection beyond the gastric lumen. The arcuate ridge surrounding the crater shows nodular excrescences as compared with Figure 11B.

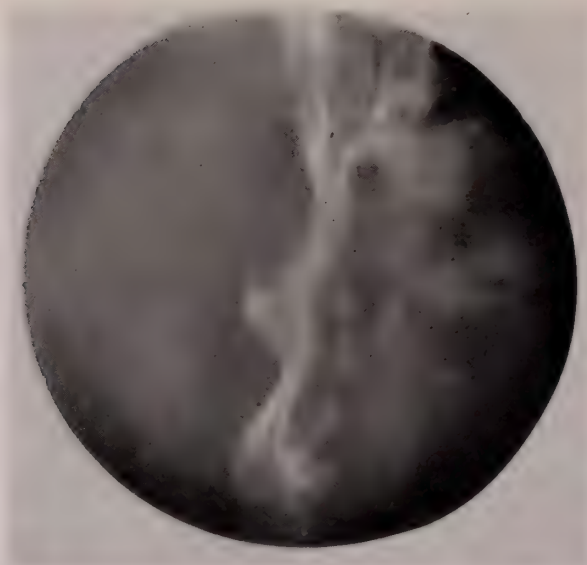


FIG. 14A



FIG. 14B

FIG. 14A, B, C. Erect spot films. Varying appearances of ulcer crater, collar and mound during filling indicate pliability of wall around the crater and exclude a rigid filling defect.

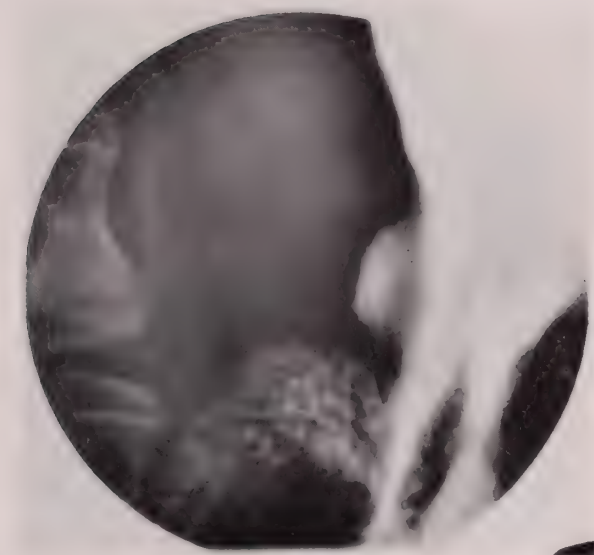


FIG. 14C



FIG. 15. Benign ulcer crater along the lesser curvature of the antrum. There is a complete curved lucent line which appears to separate the crater from the general lumen of the stomach. No collar or tunnel like communication with the general gastric lumen is seen.



FIG. 16A. Spot view with a small amount of barium and compression shows an apparent defect on the greater curvature with a crescentic patch located within its upper part. There is a thin arcuate line at the neck of this patch which resembles a Hampton line.



FIG. 16B. Many films in this case with varying amounts of barium and varying degrees of compression failed to confirm the suggestion of an ulcer crater seen in figure 16A. A variety of appearances were seen depending upon the amount of barium filling the sulci between the large number of thick folds along the greater curvature of the body of the stomach.



FIG. 17A. An ulcerated lymphosarcoma along the lesser curvature of the stomach in the region of the reentrant angle. In this view, there is a projecting crater with an apparent ulcer collar. There is rather diffuse flattening of the adjacent wall of the stomach on both sides of the crater.

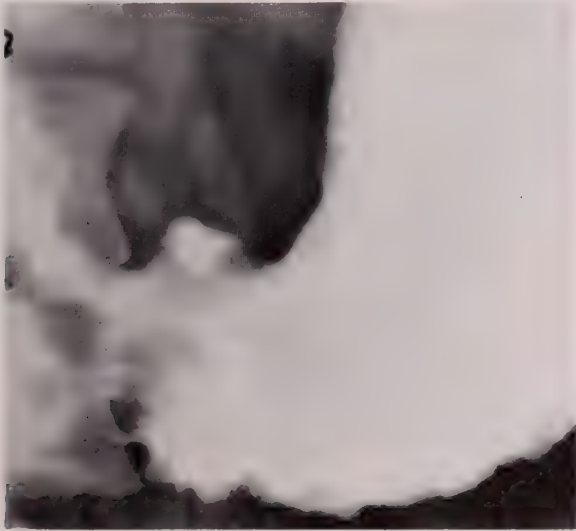


FIG. 17B. With better filling, the collar appearance is gone and the crater shows an irregular contour towards the gastric lumen side. The lucent region surrounding the crater is poorly demarcated and apparently fuses with thick folds.



FIG. 17C. Mucosal pattern study with a small amount of barium did not fill a crater but demonstrated thick multiple nodules occupying the folds about a contour defect.



FIG. 18. Hodgkin's disease of the stomach. A crater is seen in the approximate center of a rather flat defect high on the posterior wall of the body of the stomach. An ulcer collar apparently is simulated by thick folds overlying this defect.



FIG. 19. Lymphosarcoma of the exogastric type involving the lesser curvature aspect of the stomach. There is diffuse flattening and lack of distensibility of the lesser curvature with maximum indentation at a widened fixed reentrant angle. At this site, radiating folds can be seen which extend into a long neck beyond which there is a small circular collection of barium. This neck may simulate an ulcer collar but it is relatively elongated and lined by intact folds. These findings have been referred to as the "pseudo-diverticulum" type of lymphosarcoma of the stomach. A simple benign niche of this size has the appearance seen in Figure 6C.

been seen in one instance of a scirrhus carcinoma with central ulceration. Demonstration of a typical ulcer collar is also of considerable assistance in differentiating benign and carcinomatous ulceration. We have, however, observed in instances of Hodgkins or lymphosarcoma of the stomach (Figs. 17, 18) that the appearance of an ulcer collar may be simulated. In these cases, there has been additional evidence to suggest infiltration of the adjacent wall of the stomach over a considerable distance. If this associated infiltration is mucosal and sub-mucosal, irregular thickening of the folds adjacent to the crater may be seen. If the infiltration is intramural in nature, the appearance of an ulcer collar with an ulcer mound may be simulated but the defect produced is usually rather flat and diffuse. In another type of case, the collar is long and thin like the neck of a diverticulum (Fig. 19). The mucosal and intramural infiltration may be combined and diagnosis thereby facilitated.

SUMMARY

1. The classical feature of a benign gastric ulcer on roentgen examination is the projecting nature of the crater, i.e. the niche appearance.
2. Associated with a niche, there may be seen three additional features which are of importance in differential diagnosis: (a) the Hampton line; (b) the ulcer collar; and (c) the ulcer mound. These features are described and illustrated in detail.

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PRELIMINARY CLINICAL EXPERIENCE WITH E-39, A NEW DRUG FOR ADVANCED CANCER

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The ideal chemical cytotoxic agent for the treatment of malignant disease should act specifically on the cancer cell and spare the normal tissues and organs. The many chemotherapeutic agents that have been employed thus far are either not sufficiently specific for the tumor cells or else are too toxic for normal cells and produce side effects which cannot be tolerated.

The usual mode of action of the chemical cytotoxic agents is inhibition of one or more phases of mitosis with cell death occurring as a failure of cell division. Such is probably the mode of action of the nitrogen mustard group. Triethylene melamine (TEM), triethylene phosphoramide (TEPA), and triethylene thio-phosphoramide (thio-TEPA). The ethylenimines impair polymerization and thereby prevent premitotic cell formation which is necessary for mitosis. Quinones impede synthesis of ribonucleic acid and inhibit respiration and glycolysis.

The chemical agent that combines several specific phases of action would perhaps be more efficacious. Domagk has combined the ethylenimines and quinones in a single compound known as alkoxy-ethylenimino-benzoquinone and identified as E-39. This compound, in addition to the properties of its two major constituents, also has the effect of diminishing permeability of border surfaces. Experimentally E-39 causes regression of Yoshida sarcoma, Ehrlich Carcinoma, and the Brown-Pearce tumor of rabbits.

E-39 was employed clinically by Wolf and Gerlich in Bielefeld, Germany for cases of advanced cancer. Initially E-39 was used orally and by local application and was found to be ineffective. The cause of failure was the insolubility of the chemical agent. E-39 is a heavy molecule insoluble in water but soluble in alcohol. The alcoholic solution of E-39 can, however, be diluted with water sufficiently to make the preparation suitable for intravenous, intracavitary, and intra-tumoral injection without local irritation or thrombophlebitis of the injected vein. General effects such as nausea and vomiting have been only occasionally experienced but the major limiting factor in the use of E-39 is the effect on the hematopoietic system. In the experience of Wolf and Gerlich a total dose of 700 to 800 mg. administered over a period of one month in daily intravenous injections of 20 to 40 mg. is about the limit of tolerance for the hematopoietic system. Leukopenia is severe. Inhibition of myelopoiesis is first noted at the end of the second or third week of treatment or it may occur precipitously at the end of or just after completion of the course of injections. Because of the severity of the leukopenia, it is necessary that white cell counts be taken daily and that the treatment be terminated when the white cell count falls to 3000 because a

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further fall may be expected. With the leukopenia there may also occur a moderate degree of thrombocytopenia and anemia. There is no specific remedy for this severe depression of bone marrow activity. Supportive therapy with transfusions, antibiotics, and cortisone is needed for about one month when bone marrow activity may be expected to recover spontaneously.

In addition to its use intravenously E-39 was injected directly into the tumor masses either through the skin or at laparotomy and it was also used in pleural and peritoneal cavities in doses of 20 to 40 mg. in 100 cubic centimeters of saline. Orally E-39 in capsule form was administered in doses of 10 mg. daily.

In a symposium on E-39 held at a meeting of the Vienna Medical Society on December 14, 1956 most of the investigators found the drug useful in reducing tumor masses and in alleviating symptoms but there was disagreement as to whether local or intravenous injection was the better method. For our own trial of E-39 a supply was obtained at first from Dr. Wolf in Bielefeld, Germany and later from Dr. C. P. Rhoads of Memorial Hospital in New York.

CASE REPORTS

Case 1

M. T., a 46 year old white married female complained of a swollen left leg and abdominal distention for five weeks. Laparotomy in November 1955 revealed bilateral adenocarcinoma of the ovaries with extensive peritoneal implants.

A course of cobalt 60 teletherapy was administered to the abdomen from December 19, 1955 to February 17, 1956. The patient was relatively free of symptoms until about one month later when she developed ascites. Following several paracenteses and in spite of the intra-peritoneal administration of radiophosphorus (colloidal chromic phosphate) and nitrogen mustard, the patient's general condition deteriorated. There were large palpable tumor masses filling almost the entire abdomen with dilatation of the thoracic veins and swelling of both legs. Daily doses of 300 to 400 mg. of Demerol were required. Several firm metastatic nodules appeared in the skin of the right side of the chest.

On July 26, 1956 a course of intravenous injections of E-39 was begun and continued until August 7 for a total of 600 mg. At the onset of E-39 therapy the blood count and platelets were normal. On August 7 the white cell count was 5400 but on August 14 it was 1450 and it dropped to 625 on August 28. The lymphocytes varied between 5 and 10 per cent. Meticorten was given up to 40 mg. per day because of the low blood count. On September 25 the white cell count rose to 2500 and the Meticorten was discontinued. During the course of intravenous injections one of the skin nodules was injected with 3 mg. of E-39 and showed a marked reduction in size after one week. The clinical improvement was striking. The tumor masses in the abdomen were no longer palpable and the ascites had disappeared. There was only some slight residual swelling of the left leg. The patient was able to get out of bed and live an apparently normal life. She had a good appetite and gained weight. An additional 240 mg. of E-39 was given intravenously to maintain the good clinical status. The improvement continued until November 19 when a recurrence of the mass in the abdomen was found. Further E-39 therapy was administered for a dose of 170 mg., but at this time there was no favorable effect. The tumor masses continued to enlarge, the patient became bedridden again, and lost her appetite. Her pain returned and she again required 300 to 400 mg. of Demerol per day.

In spite of further E-39 therapy, Meticorten, and intravenous infusions there was rapid progression of the disease with tumor masses filling the abdomen, ascites, and edema of both legs until December 24, 1956 when the patient died suddenly.

Case 2

M. S., a 46 year old white female had an appendectomy in 1946 followed by a splenic abscess. In January 1947, a resection of the stomach was done for carcinoma which invaded the transverse colon. In April 1947, the colostomy was closed and in 1951 a ventral hernia was repaired.

The present illness began in February 1955 with an extensive adenocarcinoma of the corpus uteri treated by radiation therapy which was followed by total hysterectomy and bilateral salpingo-oophorectomy in June 1955. Subsequently there were several recurrent masses in the vagina and cul de sac which were treated with radium.

In November 1956 there was extensive recurrent disease in the vagina especially on the anterior vaginal wall with infiltration of the bladder. A vesico-vaginal fistula was present. The disease had also extended to the inguinal nodes on the left side. An intravenous pyelogram showed left hydroureter and hydronephrosis. The patient suffered severe, almost uncontrollable pain on urination.

A course of E-39 administered intravenously was begun on November 30 and continued until December 17 for a total of 490 mg. The immediate effect of the E-39 therapy was a marked diminution in pain with appreciable reduction in the amount of sedation needed. Locally, however, there was no significant change in the appearance of the neoplasm. Hemorrhages occurred frequently from the necrotic ulceration of the vagina. The white cell count which was 2900 on December 17 fell to 300 in a few days and the platelets which originally were 220,000 fell to 42,000. Transfusions were given with both stored and fresh blood. Meticorten, vitamin B₁₂, and antibiotics were administered. Temperature rose to 102 degrees. Bone marrow aspiration showed aplastic anemia and bleeding continued. It could not be controlled, and the patient ceased on January 1, 1957.

Case 3

S. S., a 70 year old female physician had a left radical mastectomy followed by x-ray therapy in 1952 for carcinoma of the breast.

In June 1956 a skin nodule over the lower sternum and metastatic lymph nodes in the right axilla were excised and the involved areas treated by radiation. Later, estrogen therapy was administered. However, fluid appeared in the left chest and paracentesis had to be done every three weeks. Intra-pleural nitrogen mustard had no favorable effect. Because the patient's general condition was deteriorating E-39 was given intravenously for a total dose of 550 mg. in 3 weeks. A dose of 20 mg. in the left pleural cavity had no immediate beneficial effect. At the end of the course of E-39 therapy the white cell count was 2300. It fell further to 170 on December 8, 1956. At that time, however, there was marked diminution in the amount of pleural effusion and the patient felt better generally. Thoracentesis was no longer necessary and the patient was in relative comfort until January 1957 when fluid reaccumulated on both sides. Nitrogen mustard was again injected into the left pleural cavity without effect. Testosterone and estrogen therapy were prescribed. Beginning January 26, 1957, E-39 was administered orally in daily doses of 10 mg. and continued to April 29. Thoracentesis was required every few weeks. Although the patient can get up and move around her general condition is deteriorating.

Case 4

S. H., a 70 year old male physician had a retroperitoneal fibromyxosarcoma which was excised in March 1952. In August 1952 a recurrence enveloping the right kidney necessitated nephrectomy. In April 1955 again a recurrence was noted and this was excised through the abdomen. In March 1956 another recurrence was removed together with a portion of the small intestine and colon. At operation all visible tumor was removed but in August 1956 a large tumor mass appeared in the right flank and right abdomen. Treatment was given with supervoltage therapy but without effect. In November 1956, 120 mg. of E-39 were given

intravenously over a 4 day period before operation. Exploratory laparotomy revealed extensive abdominal sarcomatosis with deposits involving the large bowel, small bowel, liver and omentum. The bulk of the tumor was in the right abdomen and flank. Since excision of the tumor masses was impossible, a dose of 50 mg. of E-39 was injected into the upper portion of the abdominal aorta and another dose of 50 mg. locally into the large tumor mass on the right side.

Postoperatively the patient's condition deteriorated rapidly. He developed uremia and death occurred on the thirteenth postoperative day. Autopsy was not obtained.

Case 5

A. F., a 62 year old white male had a total gastrectomy in March 1956 for carcinoma of the stomach. Subsequently an abdominal abscess developed with an epigastric fistula and severe abdominal pain. Much sedation was required, supplemented by Meticorten therapy.

On January 31, 1957 a course of E-39 was begun intravenously and continued until February 21, 1957 for a total of 210 mg. At the same time E-39 was also administered orally in daily doses of 10 mg. for a total oral dose of 170 mg. With this therapy the blood count remained within normal limits. After one week of treatment pain diminished considerably and less narcotics were needed. The appetite increased and the patient was able to sit out of bed for a few hours which he could not do previously. This remission lasted for several weeks. There is now a return of pain with gradual deterioration of the patient's general condition. Meticorten in daily doses of 40 to 50 mg. is required.

Case 6

I. W., a 46 year old white married female had a subtotal gastrectomy in 1946 for peptic ulcer. In 1951 and 1952 she suffered from papillomatosis of the bladder and was treated by frequent fulguration. In January 1956 a total hysterectomy and bilateral salpingo-oophorectomy were performed for undifferentiated carcinoma of both ovaries. Subsequently a course of x-ray therapy was administered to the abdomen and pelvis.

In December 1956, examination revealed a mass in the cul de sac with an ulceration at the vaginal vault from which a biopsy was reported as metastatic undifferentiated carcinoma. A small amount of ascitic fluid was present and the patient complained of constant abdominal pain. A course of E-39 by intravenous injections was begun on December 1 and continued to December 17 for a total dose of 410 mg. Treatments were discontinued because the white cell count fell to 3100. It fell further to 1500 on December 20 and to 1200 on January 2, 1957. Thereafter the white cell count rose to a level of 4000 to 5000. Shortly after the onset of E-39 injections clinical improvement was manifest by disappearance of pain in the lower abdomen and back and increase of appetite. Locally, in the pelvis, the mass diminished in size and the ulceration at the vaginal vault was smaller. The ascitic fluid disappeared.

Beginning on December 21, 1956 E-39 was administered orally in daily doses of 10 mg. and was continued to April 29, 1957. Because of persistent ulceration at the vaginal vault a course of cobalt 60 teletherapy was begun on February 5 and was continued to April 1, 1957. This treatment caused further improvement in the ulceration in the vaginal vault which appeared to be epithelialized. However, an induration in the cul de sac persisted. On March 26 the patient complained of severe pain in the upper dorsal spine region, marked weakness, and diarrhea, sufficiently severe to confine her to bed on April 1, 1957. Her cystitis recurred and her general condition is deteriorating.

Case 7

M. S., a 55 year old white male had a subtotal thyroidectomy in 1947 for multi-nodular nontoxic goiter. After an accident in 1950 an osteolytic lesion was found in the neck of the right scapula on routine x-ray examination. Biopsy was reported as metastatic adenocarcinoma of the thyroid gland, and review of the original goiter specimen also revealed carcinoma.

Treatment was administered with radio-iodine, 500 millicuries in 1950 and 700 mc. in 1951. In 1952 a course of x-ray therapy was directed to the right shoulder. The metastatic lesion, however, slowly enlarged. In 1955 a course of cobalt 60 teletherapy effected only slight diminution in size of the shoulder but considerable improvement in symptoms. Except for marked limitation of motion of the right shoulder there were very few symptoms and very little disability until September 17, 1956 when the patient suddenly developed paraplegia and was admitted to The Mount Sinai Hospital. X-ray examination revealed extensive metastases of the upper dorsal spine. Neurologically there was evidence of compression of the spinal cord in the region of D-1. X-ray therapy was directed to the cervical and upper dorsal spine but without effect.

Beginning on September 29, 1956 E-39 was administered intravenously daily until a total of 620 mg. had been given over a period of two weeks. There were no side effects of the treatment. The patient was sent home with his condition unchanged and he died four weeks later.

Case 8

A. D., a 47 year old white married female had a colostomy and colonic resection in April 1956 for adenocarcinoma. Subsequent closure of the colostomy was followed by a fecal fistula at the colostomy site. In September 1956 a large fixed mass was palpable in the left lower abdomen. Several small subcutaneous masses were also noted in the abdominal wall on the left side and in the right lower quadrant. The patient was bedridden and complained of severe pain in the lower abdomen and back. She was admitted to The Mount Sinai Hospital on December 10, 1956.

A course of daily intravenous injections of E-39 was begun on December 11, 1956 and continued until December 22, 1956, when the total dose was 390 mg. Her white cell count which was 8300 on December 22 dropped to 3150 on December 24 and to 350 on January 11, 1957. The platelets also dropped from a normal of 290,000 to a low of 36,000. There appeared a new complaint of pain and difficulty in swallowing which was attributed to an esophagitis, as demonstrated by x-ray studies. However, one week after the treatment was begun, there was marked clinical improvement. The patient could move easily in bed and soon was out walking around. Pain improved and much less sedation was required.

On January 23, 1957 the patient felt well, had very few complaints, and her white cell count improved to 4650. Platelets also improved to 98,000 but her hemoglobin fell to 6.9 grams. By January 31, 1957 the huge tumor mass which was palpable on admission could no longer be felt but the subcutaneous nodules were still present. One of them was injected with 7.5 mg. of E-39 and was reduced further in size. On March 11, 1957 a recurrence of the abdominal mass was noted and it rapidly grew back to its original large size. On March 19 local infiltration of 50 mg. of E-39 into the mass produced no effect. On April 3, 1957 a catheter was inserted through the left femoral artery into the abdominal aorta up to the level of L-3. Then, from April 3 until April 10 a total of 350 mg. of E-39 was injected intra-arterially. This treatment, however, had no effect on the mass. The patient's general condition deteriorated rapidly. Her white cell count fell to 1000, and on April 26, 1957 she ceased. Post-mortem examination confirmed the clinical findings.

DISCUSSION

Since E-39 was employed only in cases of advanced cancer that could not be further benefited by surgery or radiation therapy and were therefore considered to have a hopeless prognosis, the usefulness of this chemical agent can be measured only by its effect on observable tumor masses and on the well being of the patient. In these respects the effects of E-39 were noteworthy. Marked regression of carcinomatous masses was frequently observed. The patients experienced definite, even though temporary, diminution of symptoms and disability. Pleural

and abdominal effusions were suppressed. Some of these favorable effects lasted a few weeks to several months. They could not be repeated by further E-39 treatment. Eventually the patients either succumbed to their disease or were in process of doing so. The favorable effects, however, were at times so striking, even though of short duration, that further trial of this chemo-cyto-toxic agent appears to be worthy. It may be possible to get more lasting effects with either an improvement in the solubility of the drug or an alteration in the method of administration that would be less toxic to the hematopoietic system.

SUMMARY AND CONCLUSIONS

E-39 an ethylenimino-quinone cytotoxic drug was used in 8 cases of hopelessly advanced cancer. In spite of severe leukopenia induced by the drug, beneficial effects were obtained in 6 cases and were quite striking in at least 2 of them. These effects were only temporary and could not be reproduced when the patients went into relapse. They do indicate, however, that this drug has properties worthy of further investigation.

IN APPRECIATION

We wish to express our thanks and appreciation to Dr. Wolf of Bielefeld, Germany and to Dr. C. P. Rhoads of Memorial Hospital, New York for making available to us a generous supply of E-39.

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CAROTID BODY TUMORS

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Carotid body tumors are uncommon cervical tumors and considerable confusion and disagreement have existed concerning their biology and management. Their innocent clinical appearance has often lead to incorrect preoperative diagnosis, followed by an all too casual surgical approach under local anesthesia and inadequate incision. This may lead to serious and often fatal complications. It is important, therefore, that we increase the index of suspicion relative to the presence of carotid body tumors.

ANATOMY

The carotid bodies are small, paired structures, grey or reddish-brown in color, situated near the bifurcation of the carotid artery, and attached by a fine, vascular pedicle to one of the carotid arteries. Grossly, the structure is divided into lobules by projections from a fibrous capsule. Microscopically, it consists of polyhedral cells, with round or slightly oval nuclei, containing fine chromatin particles and abundant cytoplasm, which is often granular. The cells may be arranged in clusters or whorls surrounded by a supporting stroma of fine collagenous and reticular fibres, with innumerable capillaries.

PHYSIOLOGY

It was originally thought that the carotid body secretes epinephrine, an assumption based upon the presence of chromaffin granules in the cells. This is no longer considered to be so. Others theorized that the carotid body contains chemo-receptors, which respond to changes in the carbon dioxide and oxygen tensions, and the hydrogen ion concentration of the circulating blood. According to these investigators, the carotid body would thus function in association with the carotid sinus. When carotid body tumors are present, however, the absence of symptoms referable to abnormal functions of the carotid sinus, such as dizziness, fainting and seizures, would tend to disprove this latter theory. Indeed, in many humans the carotid bodies are absent, and in patients with bilateral carotid body tumors, their removal produces no deleterious effects. These facts lead to the assumption that the carotid bodies have little or no physiologic function in the body.

PATHOLOGY

The only pathology associated with the carotid body is that of tumor formation. Grossly, these tumors are reddish-brown lobulated masses, of a relatively firm consistency, ovoid or spheroid in shape, and bound firmly to the carotid

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vessels by a definite fibrous capsule. They may vary in size from 2-10 cm. in diameter. Microscopically, three types of tumors have been described. The most common variety is one in which the normal structure of the carotid body is reproduced. The second is adenoma-like in structure, in which the cells contain abundant cytoplasm and are grouped in rows or sheets, with minimal supporting stroma. The third type contains compressed crescentic, spindle-shaped cells, closely opposed to a rich capillary network, and consequently this type is called the angioma-like variety. Frequently a single tumor shows all three patterns scattered throughout the tumor.

INCIDENCE OF MALIGNANCY

Much controversy exists in the literature concerning the malignant potential of carotid body tumors. While some claim that 40-50 per cent are malignant (3), others report never having found evidence of malignancy in any of their cases (5). It is now generally agreed, however, that about 15 per cent of the cases may be malignant and manifest local invasion, regional metastasis or distant spread, this even though the histological appearance of the tumor is completely benign.

DIAGNOSIS

Symptomatology. Carotid body tumors are usually unilateral, but may occasionally occur bilaterally. The patient gives a history of a slow-growing, painless tumor in the side of the neck of months' or years' duration. The symptomatology is so insignificant and the growth so gradual, that very little attention is given the tumor until it attains sufficient size for the patient to feel that a physician should be consulted. (Occasionally, the tumor is picked up as an incidental finding during a routine physical examination.) As the tumor enlarges, it may encroach upon the pharyngeal wall and cause difficulty in swallowing. If it has invaded surrounding structures, relative symptomatology may be present (recurrent laryngeal nerve, vagus nerve, sympathetic nerves, and glosso-pharyngeal nerve). Occasionally there may be a complaint of pain, either in the neck or referred to the ear.

Physical Findings. Physical examination reveals a firm mass at the level of the carotid artery bifurcation, situated beneath the sternomastoid muscle and varying in size from 2-10 cm. in diameter. The tumor can be moved horizontally. Attachment to the carotid vessels usually prevents vertical movement. The pulsations of the associated vessels can readily be made out, but none is present in the tumor itself. We may thus summarize the physical findings associated with tumors of the carotid body by stating that these tumors should be suspected in a patient presenting a firm, deep-seated, symptomless tumor located in the upper neck anterior to the sternomastoid muscle with a history of slow growth over a rather prolonged period of time.

DIFFERENTIAL DIAGNOSIS

It is important, however, to differentiate these tumors from other tumors occurring in the same location, i.e., metastasis from a malignant tumor either

above or below the clavicle, branchial cleft cysts, neurofibromas, and primary lymphomas.

Metastatic Cancer. Thorough examination of the head and neck will usually demonstrate the primary tumor. If the metastasis is from a tumor below the level of the clavicle, some indication of this is usually given by the history and further investigative procedures can be carried out. Metastases are often rapidly growing and multiple in nature. They can be moved in *both* lateral and vertical planes and, unless extremely large and fixed, can be separated from the carotid artery.

If metastasis arises from carcinoma of the thyroid, one or more nodules may be felt in the thyroid. These metastases are usually softer than carotid body tumors, are unattached to the carotid artery (except in very late stages) and can be moved in all directions.

Branchial Cleft Cysts. These most frequently occur below the level of the carotid bifurcation and as they enlarge they become more and more superficial. They, too, can be moved both in a vertical as well as in a lateral plane, and aspiration reveals a characteristic yellowish fluid.

Neurofibromas. It is often extremely difficult to differentiate carotid body tumors from neurofibromas. The latter may arise in the region of the carotid bifurcation, but most often occur further laterally. They may be extremely firm and are usually more mobile.

Lymphomas. While primary lymphoma may occasionally occur as a single mass in the neck, the history is usually one of rapid development followed by the appearance of other nodules in the vicinity of the original mass or elsewhere in the body.

A well performed aspiration biopsy can often either prove the diagnosis of carotid body tumor or differentiate other causes of the neck mass.

TREATMENT

It is imperative that the true nature of the tumor be recognized prior to an attempt at therapy. A causal approach, an inadequate incision and improper preoperative preparation may lead to a hazardous situation. The tumor tends to encircle the common, internal and external carotid arteries and become fixed to these structures. This tendency of fixation to the vessel wall has added considerable gravity to their proper management and in the past, surgical intervention was attended by a forbidding mortality of 40-55 per cent. As a result, surgeons were loath to attempt surgical removal and adopted an attitude of "watchful waiting." Today, the situation has altered considerably. Newer concepts of the anatomy and physiology, and improved surgical techniques, have decreased the mortality and morbidity previously reported, and surgeons now will attempt extirpation of the tumor.

Preoperative Evaluation. It is advisable that a preoperative neurological examination be performed so that any post-operative neurological findings can be properly evaluated. A carotid angiogram may give valuable information concerning the patency of the Circle of Willis and in some clinics preliminary carotid compression up to ten minutes four or five times a day is practiced in

order to increase the collateral circulation to the brain. Unfortunately, the ability to tolerate carotid compression and an angiogram showing a good Circle of Willis, does not always insure against the development of a vascular accident following ligation of the common or internal carotid arteries. Warren reported fatalities after ligation of the carotid vessels in 3 of 7 patients in whom preoperative carotid compression was without incident. To prepare against such a possibility, the family of the patient must be apprised of the dangers inherent in the operation.

Surgery. Removal of the carotid body tumors is concerned with two problems: Can the tumor be extirpated without injury to the vessel? Must the artery or arteries be sacrificed?

If the latter condition holds true, can anything be done to maintain the continuity of the vascular channel and thus assure an adequate blood supply to the brain?

Gordon-Taylor and later, Morfit, helped answer the first question by demonstrating that the carotid body develops in the adventitia of the carotid artery and it is here that the carotid body tumor is found (2, 7). Very careful dissection in the adventitia or between the adventitia and media of the vessel may thus allow for removal of the tumor while leaving the vessel intact. Even in cases of extremely large tumors which completely encompass the common, external and internal carotid arteries, it is often possible to remove them by careful dissection in the serosal plane of the vessels.

In the event that the tumor cannot be removed without sacrificing the common or internal carotid arteries, every attempt should be made to re-establish the continuity of the vascular channel and thus maintain an adequate blood supply to the brain. If a carotid artery homograft is available, it offers the greatest facility for replacement. Autogenous vein grafts have been used, but with a lesser degree of success. More recently, artificial prostheses have been employed with gratifying results. End-to-end anastomoses between the cut ends of the common carotid and the internal carotid arteries is often feasible, even if a segment of artery as long as two inches has been removed. This is facilitated by cutting the external carotid artery at the carotid bulb, a maneuver which allows the course of the common artery to change from a curve to a straight line, thus frequently approximating the cut ends of the vessel.

COMPLICATIONS

It is obvious that when the tumor can be removed without excising either the great vessels or the adjacent nerves, the complications should be almost negligible. If the common or internal carotid arteries are ligated, the major hazard is cerebral damage which can be so severe that it progresses to coma and death.

Lesser degrees of cerebral damage are manifest by neurological complications and these may appear immediately upon ligation of the vessels or as long as six days afterwards. They vary from a transient weakness or a monoplegia of the upper extremity to a contralateral hemiplegia, the most common finding. Transient dysarthria, dysphagia, ipsilateral optic nerve atrophy, contralateral

temporal hemi-anopsia and varying degrees of aphasia (if the left side of the brain is affected in the right-handed person and vice versa) have also been known to occur.

The differences in the complications developing in different patients can best be explained by variations in the cerebral blood supply. For a patient to undergo a carotid ligation without either succumbing or suffering cerebral disability, there must be an anatomically efficient collateral pathway through the Circle of Willis and an absence of arteriospasm, either diffuse or segmental.

In reviewing the results of a series of 88 consecutive carotid ligations from 1926 to 1952, Moore and Baker found an over-all mortality rate of 30.6 per cent with 45.4 per cent cerebral complications (6). Of interest is the drop in the operative mortality from 55 per cent (on those cases performed in 1926 to 1937) to 11.4 per cent (cases done in 1948 to 1952). Concurrently, the cerebral complications fell from 60 per cent in the earlier group to 31.4 per cent in the later period.

Their studies revealed that the one common factor in a significant number of cases suffering major cerebral complications was hypotension, either during or after the surgery. In those patients suffering little or no ill effects from ligation, hypotension occurred in only a few. Maintenance of a sustained normal arterial pressure and blood flow to the brain thus plays a most important role in the prevention of the complications following carotid ligation.

If, during the removal of a large carotid-body tumor, it is necessary to resect some of the nerves in the area, other complications occur. Resection of the vagus nerve causes paralysis of the palate and vocal cord on the involved side, and pharyngeal anesthesia. A tracheostomy is often necessary until the patient has learned to swallow without aspiration. Resection of the hypoglossal nerve causes paralysis of the tongue on that side followed by atrophy, thickened speech and difficulty in deglutition. The patient often learns to accommodate to this condition. Resection of the spinal accessory nerve creates a dropped shoulder with shoulder girdle weakness, and lysis of the sympathetic chain leads to a Horner's syndrome.

CASE REPORTS

Two cases, one having a benign tumor and the other a malignant tumor, will be presented in an attempt to illustrate the problems encountered in diagnosis, preoperative preparation, operative procedure and post-operative management.

Case 1

A. S., a 22-year-old Puerto Rican male was admitted because of a mass in the left side of his neck of two years' duration. The mass had been slowly increasing in size and only recently was associated with some pain and a feeling of pressure. Since the onset of the mass he had been treated intermittently at four other hospitals with anti-tuberculous drugs for a "tuberculous adenitis", this in spite of repeated negative gastric washings, guinea pig inoculations and chest films.

On admission the positive findings were limited to the left neck which contained a firm, smooth mass, 8 cm. in diameter, located beneath and anterior to the upper half of the sternomastoid muscle. The upper margin of the tumor extended to the angle of the mandible.

Although the mass was slightly compressible and appeared to have a pulsation, it was difficult to ascertain whether or not the transmission was transmitted. No bruit was present. The mass could be moved horizontally but not vertically, and was found to push the left side of the pharynx inwards. No palpable lymph nodes were present, the thyroid contained no nodules or areas of thickening, and the examination of the oral cavity, pharynx, larynx and nasopharynx revealed no evidence of a primary tumor. There were no findings pointing to a tumor below the level of the clavicle. Laboratory work-up was entirely normal. One week after admission, an aspiration biopsy was performed and the tissue was reported as "fragments of carotid body tumor."

Preoperative neurological evaluation revealed no abnormalities, and the patient was able to withstand compression of his left common carotid artery for over fifteen minutes without any untoward effects. The patient was prepared for surgery, and an arterial homograft was made available in the event that it was found necessary to resect the vessels.

At operation the tumor was found to completely encircle the common, external and internal carotid arteries and extended from one and a half inches below the bifurcation to two inches above, the upper limit of the mass being deep to the angle of the mandible. Some tumor tissue was found extending down along the common carotid artery from the main mass. The tumor was extremely vascular, but it was possible to remove it by careful dissection in the adventitia and between the adventitia and the media of the vessels. Two small openings on the posterior aspect of the bulb were repaired with fine arterial silk sutures. The patient withstood the operation very well and post-operative neurological evaluation revealed no defects. Except for a slight wound infection, his course was uneventful. The pathology report was "carotid body tumor."

This case presents several interesting features. It is obvious that the incorrect diagnosis was made at other hospitals, and as a result the therapy he received during the first two years was ineffective and the mass continued to grow. When he was admitted to Mount Sinai Hospital, the history of a gradually enlarging, asymptomatic mass in the neck and the physical findings raised the suspicion that this might be a carotid body tumor. An aspiration biopsy was performed, and when the true diagnosis was apparent the patient was adequately worked up, prepared, and the necessary blood and arterial homografts were made available. By understanding the gross anatomy of the carotid body, it was then possible to remove a tumor which, on first glance, appeared non-resectable, without excising the carotid vessels.

Case 2

G. T., a 22-year-old white male who was first seen in February 1957, because of a gradually enlarging mass in the left side of his neck of one year's duration. There was no pain associated with this mass. At times there was slight variation in its size. Many physicians had been consulted but no diagnosis had been made. Examination revealed a 3 x 3.5 cm. rather irregular mass anterior to the edge of the sternomastoid muscle at the junction of the upper and mid thirds. Some areas were firmer than others. The mass was somewhat movable, but gave the impression of having a moderate amount of inflammatory reaction around it. There was no pulsation associated with the mass. No other masses were present in the neck and there was no displacement of the pharyngeal wall. Although the diagnosis was not definitely apparent, it was the impression that this might represent either a tumor associated with the submaxillary salivary gland, a branchiogenic cyst or a carotid body tumor. Surgical excision was advised but the patient delayed until May, 1957, when he was admitted to the hospital. Physical examination was essentially the same and the laboratory work-up was completely normal. Operation was performed the day after admission. The presenting tumor was found to be a mass of nodes, which were submitted for frozen section. All the pathologist would say was that it represented some form of anaplastic malignant tumor, the exact nature of which was unknown. He suggested waiting for a paraffin section report. Deep to the nodes that were removed, there was a firm mass that seemed to be adherent to the surrounding structures.

Because the exact nature of the neoplasm could not be determined either by frozen

section or by exploration, and because this might represent one of the lymphomas, it was decided to wait for a formal section. The margins of the tumor were rimmed with silver clips which would allow for accurate radiotherapy if lymphoma was found to be the diagnosis.

Two days later the pathologist reported "carotid body tumor showing marked fibrosis; lymph nodes showing metastatic carotid body tumor."

Following the pathology report, the patient was taken to the operating room, five days after his first operation, for a radical neck dissection and resection of the carotid body tumor. Preparations had been made so that a graft could be performed if it were necessary to excise the carotid vessels. The radical neck dissection was performed in the usual manner, but the tumor could not be separated from the carotid vessels, even by dissection between the adventitia and the media of the vessels. A two-inch segment of the vagus nerve was intimately "fused" with the tumor. Excision followed by a vascular graft was then considered, but the tumor along the vessels extended two inches above the level of the angle of the mandible, thus making the upper anastomosis non-feasible. It was the impression, at the time of surgery, that the tumor also invaded the upper end of the internal jugular vein at the base of the skull, and this mitigated against proceeding with excision of the vessels without replacement grafting. The parents of the patient, incidentally, stated post-operatively that they were unwilling to undertake the risk of mortality or cerebral complications entailed in carotid ligation.

At the end of the procedure a small plaque of tumor remained surrounding the carotid vessels and vagus nerve, from one and a half inches below the bifurcation to the base of the skull. The patient did extremely well and was discharged on the eighth post-operative day. He is at present receiving cobalt tele-therapy.

This second case highlights the importance of early surgical intervention, despite the lack of symptoms. Although his tumor was of shorter clinical duration and smaller in size than that in the first case, it was no longer benign, had already metastasized, and was actually non-resectable. This case shows dramatically that the histology of the tumor may appear perfectly benign, even though it is actually malignant and capable of metastasizing.

SUMMARY

The existence of a carotid body tumor, though uncommon, should be considered as a possibility in any case which indicates a slowly enlarging, usually asymptomatic mass in the region of the carotid bifurcation. Continued local growth can lead to encirclement of the common, external and internal carotid arteries. Although they are generally benign, they *may be* malignant and give rise to regional lymphatic spread or to distant metastases. Surgical removal is therefore recommended.

Surgical excision is usually feasible by careful dissection in the adventitia because the carotid body arises in the adventitia of the vessels and the tumors rarely penetrate the media or the intima. Every attempt must be made to maintain the carotid blood flow to the brain. The complications arising from the interruption of this blood supply are discussed. Two cases, one benign and one malignant, are presented.

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A CASE OF RECURRENT MALINGERED PLACENTA PREVIA

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CASE REPORT

One of us (A. F. G.) was first consulted by a 24-year-old woman and her 27-year-old husband on June 13, 1954. She had been delivered of her three previous pregnancies by caesarean section. The dual purpose of the visit was to ask whether a fourth caesarean section would be mandatory when she had her delivery and how soon after her recent caesarean section another pregnancy was permissible. The reproductive history follows:

1951, in the first year of marriage, at the beginning of the ninth month of pregnancy, she was delivered by caesarean section because of "placenta previa". The four pound, eleven ounce daughter survived. 1952, when six and a half months pregnant, she was again delivered by caesarean section for a second "placenta previa" of a three pound, two ounce child who died after 24 hours. On December 2, 1953 when eight months pregnant she had a third caesarean section for a third "placenta previa", the three pound, seven ounce infant expired after twelve hours. The three operations were performed in another hospital by a general surgeon. On questioning we elicited the fact that the patient bled intermittently throughout all three pregnancies.

The physician who had done the three caesarean sections for recurrent, perhaps one might say, "chronic placenta previa", confirmed the whole story. He too marveled at the coincidence of one patient having three "placenta previas". He told us that the third infant was anencephalic.

The patient first consulted us six weeks post caesarean section, in the midst of her first postpartum menses. Naively believing the story, we counselled a hystero-gram. We also advised contraception until six months postpartum. She was next seen two and a half months later, April 3, 1954. Last menstrual period was March 1st. No hystero-gram had been done and contraception had not been attempted.

After examination she returned to the consultation room and said, "I have something to tell you".

She confessed that the whole history had been a complete fabrication. She had read that labor could be induced by puncturing the membranes and in her first pregnancy, becoming "very tired of being pregnant", she took a long hat pin and attempted to rupture the membranes. Instead of rupturing the membranes, she began to bleed freely. Her obstetrician was summoned, who sent her to the hospital by ambulance. While preparations were being made for

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caesarean section, the bleeding suddenly ceased. Intent on being delivered and fearing to be sent home, she got out a knitting needle and succeeded again in producing sufficient bleeding to justify the caesarean section. As stated, the four pound, eleven ounce baby survived.

When next pregnant, at the sixth and a half month, she was seized with an uncontrollable urge to terminate pregnancy. She resorted to the hat pin technique with the same result; a caesarean section for a misdiagnosed placenta previa. The three pound, two ounce male infant succumbed within 24 hours. The third pregnancy was allowed to continue approximately as long as the first, which yielded her only living child. Again by self-manipulation she induced bleeding with the resulting caesarean section. This three pound, seven ounce child also succumbed; she has never known it was anencephalic.

The reason she divulged these obstetrical facts was to protect herself against similar self-mutilation. She felt since we knew the story, it would be pointless to try to fool us, therefore, she would have no incentive to induce bleeding during her current pregnancy. After much pressure the patient consented to visit the psychiatrist (M. L. G.). The course of pregnancy was stormy. In early pregnancy she had bouts of vomiting and paraumbilical pain. She complicated diagnostic examination by holding her abdominal muscles in board-like rigidity. She admitted taking ergotrate during the fourth month of pregnancy with no sequelae. During the fifth month she and her only child either deliberately or accidentally walked into the path of an automobile. Later in the month she complained of vaginal bleeding and the introitus was found blood-stained. It was thought wise not to seek the source of the bleeding but simply to take for granted the bleeding was self-induced. In the fifth month she claimed to have had chills and fever up to 101 degrees. Catheterized urine was negative. In the sixth month she bled again; this too was treated by obstetrical indifference. Her due date was December 8, and in order to protect her from further self-mutilation she was admitted to The Mount Sinai Hospital from 10 8 to 11 7. Despite this, during her prenatal stay in the hospital she intermittently traumatized her vaginal organs with sharp objects; on another occasion she forced the thermometer up to 103 degrees F. By now she had carried the fetus longer than any of the other three. She was excited and went into unpredictable panic states. Tranquilizing drugs were given and a date for caesarean section selected. After the selection of the specific date, 11 26, the patient became calmer and asked to go home, assuring us she would not injure herself. In the 17 day interval until readmitted she got along satisfactorily with the support of telephone calls and office visits. She was readmitted 11 24 and signed permission for operation and tubal ligation.

When the date of operation arrived she became both hostile and alarmed. We quote from the resident's note. "Patient bleeding during the night. Brought to K2 (delivery floor). Hat pin taken from patient. Patient refuses section. Says she wants a vaginal delivery. She refused preoperative medication. Bit and scratched nurse." Later note. "Patient agreed to section after she was seen by Drs. A. F. G. and M. L. G. Hgb 11.0 gms."

A classical caesarean section was done under spinal anesthesia. Bilateral tubal ligation was carried out with difficulty due to adhesions. The convalescence after operation was uncomplicated. The patient seemed happy and took a normal interest in her six pound, two ounce son who was bottle fed.

She was next seen on 6 26 55 with the complaint of swelling of the right thigh beginning 2 months post-delivery. She was referred to a surgeon of our choice but went to her own, who did a local excision on 11 24 55. Pathology report: fibromyosarcoma. She then consented to go to the surgeon originally recommended, who did a radical amputation with a right hemipelvectomy several days later. She has been fitted with a prosthesis and walks quite well. She was last examined on 6 29 56 with complaint of vaginal bleeding whenever the false leg was worn for a protracted period. Physical examination was negative and she was advised to continue to wear the leg. She was last spoken to in January 1957 when she reported she was well.

PSYCHIATRIC HISTORY

The patient is the older child in a family of two, her brother being four years younger. Both parents are dead. She is a high school graduate and has had two years training as a psychiatric occupational therapist.

The essentials of the family history are: Her father died in 1940, aged 60, from carcinoma of the lung. He had severe diabetes, its complications had necessitated a bilateral leg amputation at the knee joint. The patient, who was then 7 years old, said she was terrified by the conviction that her father's amputated legs were hidden in the cellar. His actual death was described by the patient as a vivid and traumatic event. She had gone to school as usual that morning and as she left some oxygen tanks were being brought into her father's room. This was the last time she saw him alive, for that afternoon when she came back from school, she states she found him sitting dead in his chair. She did not speak to her mother for several days, blaming her for allowing her to go to school under the circumstances.

Her only sibling, four years her junior, contracted poliomyelitis in 1941 when he was seven years old and became paralyzed below the waist.

Her mother died at 43 when the patient was 18. Her manner of death, which was to play a crucial role in the patient's subsequent attitude and behavior, was revealed by her in clinical, impersonal language. It seemed clear that much was repressed or distorted. The patient stated, "Mother died of a complete loss of blood, which came out vaginally during her menopause. . . . She died in one hour—I was with her when she died and was terribly frightened. Although I was supposed to consult a psychiatrist one year before, I didn't do it until after mother died—and then I waited 6 months."

Shortly after her mother's death the patient indulged in her first deliberate malingering. She successfully simulated an attack of acute appendicitis and had an appendectomy by the same surgeon who later performed the first three caesarean sections.

At the first psychiatric interview, the patient somewhat sheepishly told the

therapist that since no one in her family knew anything about her former gestures of deception, including the bleeding, they, if for no other reason, would not approve of her visits to a psychiatrist. In addition, she stated that no one in her family, neither her husband nor parents-in-law had any use for psychiatry and that she would be stigmatized and very likely penalized, in some way or another, were she to disclose her visits for psychotherapy.

Her main concern was being 3 $\frac{1}{2}$ months pregnant; she would for the fourth time be powerless to resist the urge to initiate premature delivery. She furtively and rather slyly stated that she had already selected a pair of long-handled scissors and a knitting needle and had hidden them safely so that they would be available when she felt compelled to use them. She tried hard to emphasize the fact that not only did she not wish to kill her unborn babies, but quite the contrary—she was so anxious to have them, that one reason for her taking matters into her own hands was her impatience to terminate the pregnancy in order to see her baby, born, and detached from her. She showed no knowledge, and little interest in the question of viability, indicating such extreme naivete that it was suspected that this blind spot was not the result of ignorance, as much as repression of facts with which she did not choose to be conversant.

Her next significant remark was that her aunt, shortly before her marriage, put the "hex" on her by prophesying that all babies she might have would die! The psychiatrist, at first impression, was inclined to regard her psychopathy to be her outstanding psychiatric difficulty, but began to be increasingly impressed with the paranoid features the patient exhibited. Her need to exploit her activities, most of which she verbalized apologetically, was clearly irresistible. This was particularly obvious when she showed her satisfaction at the therapist's awareness of what she had done in order to terminate her pregnancies. The masochistic-sadistic interplay thus at once assumed a conspicuous role and in many subsequent sessions never lost its prominence. She did her best to amaze, baffle, and particularly shock the psychiatrist and reacted with discernible disappointment when he did not take her bait, as he tried not to indicate his astonishment, and certainly not his disapproval. This lack of criticism was either not what she had anticipated or wished for, so she made herculean efforts to convince the therapist that she was evil and selfish, and accordingly deserved punishment. Since the psychiatrist sensed that his patient had already been punished not only by her own conscience, but by incessant disparagement and criticism by her parents-in-law (who had always made her feel inadequate and inferior) every therapeutic effort was made to lessen a load which had long ago become top heavy.

Her many visits to the psychiatrist had to be clandestine, since her husband, intimidated and dominated by his family, refused to give his wife any money for this purpose, on the grounds that psychiatry was "bunk" and in any case, not for her. Because of this prohibition, the patient had great difficulty in making and keeping her psychotherapeutic appointments. Being forced to lie, she usually told the family she was seeing the obstetrician and occasionally varied the prevarication by stating she had to have a session with her dentist. Disturb-

ing for the most part as was this constant need for intrigue and concealment, it was not altogether repugnant to the patient. In some measure it fitted appropriately into her own scheme of intrigue, confabulation—the game at which she was so apt, of distorting facts and fooling people—in this case her family.

Since it was impossible to reveal the patient's confidential confessions to her husband, neither he nor the rest of his family was aware of the great danger that the patient would repeat her attempts to end her present pregnancy as she continuously threatened to do. On August 9th the psychiatrist, wishing an independent psychological evaluation, referred the patient to the clinical psychologist (F. B.) without disclosing the reason for referral. The summarized report stated:

"Regressive manifestations are conspicuous in conjunction with alternating periods of control and reckless impulsivity. She is only superficially influenced by interpersonal relations and reveals dominant masculine strivings concomitant with rejection of the feminine role. This pattern is underpinned by pervasive passive-dependency cravings comprising resentment over having to play an adult role, frustration of parasitic demands, and early disruption of a normal child-parent relationship. She is unable to live out either of these roles because of vivid sado-masochistic fantasies and drives, an impasse which contributes to marked personality disorganization.

The weakness of her inner controls and her resistance to responsible behavior-modifying introspection leaves her with no defense against impulsive acting out of her autistic fantasies. This is augmented by the absence of restraining object relations within a context of psychopathic character distortion and schizophrenic emotional blunting. Sporadic guilt reactions appear, but have little effect upon her behavior because of their shallowness.

Unstable and transitory identification with parental figures set her apart from people and deprives her of the capacity for empathic relationships. This is associated with a desperate effort to retain narcissistic individuality by renouncing any type of object relationship which might remotely detract from her own fragile ego. To this extent the hostility she manifests toward foetal symbols in the Rorschach represents an attempt to preserve her precarious sense of identity and infantile omnipotence by quickly extruding a potential competitor, with a subsidiary urge to destroy the ambivalently regarded and introjected mother figure with whom she does not wish to identify herself. Hence, regarding herself as having been rejected by the hated mother whose gestures of affection she considered insincere, she now reverses the role through an indirect and devious identification, which culminates in a complex expression of pan-destructiveness.

Her desperate and wounded narcissism cuts her off from meaningful human contacts and accentuates the picture of wilfull rebelliousness which conveys the psychopathic component of her personality. But her blunted effect, inflated infantile omnipotence, diffuse and impermanent object relations, and her poorly integrated ego give ample evidence of a chronic ambulatory schizophrenia obscured by conspicuous sado-masochistic psychopathic acting out of autistically motivated impulses."

PSYCHIATRIC DISCUSSION AND FORMULATION

In an attempt to ascribe significant meaning to this patient's repetitious attempts to precipitate birth, one becomes aware of not *one*, but a *number* of motivations. Perhaps her outstanding need was to destroy. In spite of her protestations that she avidly wanted her babies, her feigned ignorance, (which "translated" meant lack of concern for) the obvious non-viable status of the fetus seems clearly to point up the raging conflict between her conscious verbalizations and her unconscious (repressed) wishes.

A second theme which seems dominant is that she was indeed a "trapped" woman. "Trapped" and inextricably enmeshed in what was really an untenable domestic and marital morass, in which, in order to survive, she had to yield at almost every point, thereby subjecting herself to an un-ending relinquishment of both dignity and status, as well as the severest narcissistic deprivations. She was cherished by no one.

Thirdly, the ambivalent but close identification she maintained with her own deceased mother and father, whose deaths were synergistically traumatic in their timing as well as their nature, wounded, and later scarred what was even at the time, a fragile and unusually vulnerable ego. Thereafter, her feeble defenses virtually collapsed, and since she could no longer do battle with her realistic, interpersonal, and environmental entourage, she seized upon her doctors as the only attainable target.

To deceive, baffle, and create anxiety in her physicians became an obsessive, compulsive necessity, and her early successes (dating from her malingered appendicitis) admirably served her sadistically oriented, neurotic drives which at this point could no longer be denied.

She presented a picture combining both psychopathic and schizophrenic elements, (the psychological study corroborates the almost inextricable blending of the two patterns) one predominating at one time, the other at another, when its ascendancy served her purposes better. In retrospect, however, this woman must be regarded as psychotic.

She remains a complicated and defeated woman whose masochistic, sadistically compulsive needs seem to be relatively, but only temporarily, appeased. Prognostically, only the most pessimistic speculation seems justifiable, since it can be reasonably predicted that "acting out" of her destructive drives will almost certainly be recurrent.



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FOREWORD

When the time came to take cognizance of the retirement of Dr. Paul Klemperer from active status as Pathologist to The Mount Sinai Hospital, there came an insistent demand for a Festschrift, to meet the need of his pupils, colleagues and friends to verbalize their feelings for this great and kindly man. Not for generations has any man at this hospital, which has produced so many great men, commanded such loyalty, devotion, affection and love. His is the unique power of communicating to the humblest neophyte a feeling of shared enthusiasm for the acquisition of knowledge, and of filling each pupil with his own joy and zeal for learning, not as a chore, not as a duty, but as a God-given privilege.

An old Hebrew folk myth holds that the very existence of the world depended upon the Lamed-vovniks, thirty-six righteous men found in all ranks of society from the humblest to the highest, not disguised but not flaunting their status, and constrained to admit their identity when questioned. Supposedly they could be recognized by the shine in their eyes and their aura of saintliness. They were saints: wordly, not withdrawn—robust, not frail—sanguine, not anemic—heartly, earthy, vital, alive. Klemperer is one of these, and to him we dedicate this Festschrift, the traditional Central European tribute to a great teacher. We hope that as a student and “Assistent” of the great Sternberg, a member of the Viennese school of pathologists in direct line from Rokitansky, Dr. Klemperer will find the form of the tribute sympathetic and welcome. In any event, this is truly a volume that *had* to be written by his many devoted pupils and by his friends.

L. R. TUCHMAN

PAUL KLEMPERER—AN APPRECIATION

ELI MOSCHCOWITZ

New York, N. Y.

"Take an interest I urge upon you in these holy dwellings to which the expressive name of laboratories is given. They are the temples of the future. It is there that humanity grows bigger, strengthens and betters himself.", Louis Pasteur.

No appraisal of Paul Klemperer's services to pathological anatomy can be just without an inquiry concerning the influences that moulded his career. Such an inquiry illustrates how small happenings, more or less in the nature of accidents, can govern one's destiny. Paraphrasing "Dear Brutus", success is often the result of a series of fortuitous accidents. His home environment was conducive to the pursuit of a profession. Klemperer's father, a lawyer, had a deep respect for a professional career and Klemperer's first impulse was to follow his father's footsteps; he actually began the study of law. Then occurred the first apparently inconsequential incident that shaped Klemperer's future. He attended a lecture given by a man named Sigmund Freud. This was in 1906, when Freud was but a voice crying in the wilderness. Klemperer became one of his first disciples, an event that endowed Klemperer with a modicum of immortality, since in the second volume of Ernest Jones' authoritative life of Freud, Klemperer is mentioned no less than three times, once even as deceased, which, to say the least, according to Mark Twain, is gross exaggeration.

He became a member of the newly organized psychoanalytic society, and was chosen by Freud to report on congresses, meetings, etc. Klemperer pursued psychoanalysis purely as a hobby and it was only after he began the study of medicine that he thought of psychiatry as a specialty.

This episode in his life is already symptomatic of that trait which distinguishes Klemperer both as a pathologist and as a man—his innate humanism; for no matter what one may think of psychoanalysis, its approach is surely a human one. His interest in Freud was instinctive and may be viewed as the implantation of a seed upon a fertile mind. It comes as no surprise that shortly thereafter Klemperer shunted his yearnings from law to medicine. In 1906 he matriculated with full intention of becoming a psychiatrist. In time his interest in psychiatry as a vocation waned, because he felt that therapeutically it had too many limitations. His ambition shifted to becoming a family physician, modeling himself on the lines of his dear friend and family doctor, Dr. Rudolph Kaufman. Here again one senses his strong humanistic urge. The probability is great that the world lost a first rate family physician had his ambition not been diverted. To attain this end it was essential, according to University custom, to become a "privat docent."

Then occurred another trivial incident that shaped Klemperer's career into the lasting framework which he has since adorned: a friend suggested that he study pathology for a year. He had no particular leaning at that time toward this science but he grasped an opportunity to work as a volunteer with Karl Stern-

berg who was pathologist in Brünn, renowned as the site of the monastery where Mendel founded the science of genetics. It was a fortunate choice because Sternberg was not only a pathologist of distinction, but an imaginative and stimulating figure. After seven months a vacancy occurred and Klemperer was offered an assistantship which obligated him to work for another year. Up to this time Klemperer viewed pathology merely as a stepping stone toward his docentship but the close intimacy led to interest that determined him to choose pathology as his life work. He was appointed Assistant in Medicine to a large Hospital in Vienna when the first world war broke out. He served for the full four years as an army pathologist, where he had an extensive experience with infections such as glanders, cholera, typhus, etc. Providentially, he recovered from an attack of epidemic influenza in 1918 when he was 31 years old. The following year at Sternberg's invitation Klemperer returned to work in Brünn and later became his assistant in the Wieden Spital in Vienna.

In 1921 Klemperer emigrated to America, because he felt that as a Jew his future in Vienna was limited. Through the efforts of Dr. Jobling he was appointed assistant Professor of Pathology at Loyola University in Chicago. His first job was to clean the windows and he has been cleaning mental windows ever since. Here at Loyola he taught pathology and simultaneously served as pathologist to the Mercy Hospital where he saw little but surgical pathology. Dissatisfied and drawn to New York by his family, he grasped an opportunity offered by Ward J. McNeal to become assistant Professor of Pathology in the New York Post Graduate School of Medicine. After a few months refresher course in Vienna, he began his duties in 1923. He served three years but during most of the time he felt bored; he missed intellectual stimulation.

These years in the Post Graduate Hospital proved fruitful in one respect: there he discovered and imported to our Hospital our beloved Sadao Otani. He and Klemperer were to become the Castor and Pollux in the Mount Sinai firmament.

Up to this time Klemperer was a steady but not a prolific writer. His first article, published in 1914 on "Zwischenzellen Sarkom des Ovars," already foreshadows his keen, scholarly, incisively logical and independent exposition.

In 1926 in collaboration with Drs. Kilian and Heyd his study on the pathology of catarrhal jaundice was published; this sounded the death knell of this disease as an anatomical entity. This paper proved to be an "open sesame." At this time another fortunate circumstance arose; the position of Pathologist to our Hospital became vacant. As a candidate Klemperer was invited to lecture on his subject in the Blumenthal auditorium where he proved that besides his other attested qualifications, he knew how to teach. He was appointed in 1926, and has been with us ever since.

These thirty years have encompassed momentous changes in medicine. The vast piling up of factual data, tests, etc., has resulted in an arborization of medical thinking, mostly due to newer and more refined instruments of precision, that is bewildering in its complexity. Little wonder that specialization has become more necessary than ever, so that now there are specialists within specialists. The

ultramicroscope is the symbol of this drift and who has the temerity to believe that this instrument has attained its ultimate refinement? One speculates whether the human mind can keep the pace.

One need not be enamoured of the "good old days" to realize that clinical medicine has lost much of its humaneness even despite the invasion of psychosomatic medicine. A patient is no longer a living, breathing, loving, hating individual, but an inchoate mass of tests. It is not surprising, therefore, that compensatory mechanisms have arisen and some of the best minds have tried to formulate broad generalizations that are easier to cope with. No one is more keenly aware of this movement than Klemperer. As he once phrased it in homier words, it is a question of "splitting" or "lumping." It is to the "lumping" urge that we owe such concepts as nephrosis, reticulosis, lymphomatosis, diffuse vascular disease, hypersplenism and other organic hyper and hypo functions. This is not the place to look these gift horses in the mouth, albeit the abuse of these concepts leads only too often to complacency, if not to intellectual sterility; but as concepts they have often borne fruit.

The pattern of thought in Klemperer's publications in these thirty years parallels closely that of the course of medicine. The earlier ones represent substantial accessions of facts in an exceptionally broad field of morbid anatomy; the latter belong largely to the "lumping" kind, climaxed by his widely accepted concept of the collagen diseases. Curiously this concept was born of a misinterpretation of fact and it is a tribute to his intellectual courage and integrity that he openly retracted.

In the process of parturition during his factual splitting period, Klemperer made a number of substantial contributions that will surely endure. I refer as examples to such studies as that on cavernous transformation of the portal vein (1928); on malignant nephrosclerosis written with Otani (1931); the morbid anatomy of that peculiar entity termed "thrombotic thrombocytopenic purpura" (1936); chronic intrahepatic obliterating cholangitis (1937) and giant follicular lymphoblastoma in which he collaborated with George Baehr (1940). These were all pioneer studies. Nor may one ignore his monograph on the spleen, published as a comprehensive and critical survey of the finer structure of the organ and the morbid anatomy of splenomegaly. After years, it stands as a classic. In passing one must admire the erudite and refined phrasing of his articles, particularly as he is writing in a foreign tongue.

It is interesting to observe that with the passing years his publications are broader and more philosophical and spiced with abundant seasonings of wisdom. The human quality pervades not only Klemperer's writings but also his expositions at our never to be forgotten clinical pathological conferences on Wednesday afternoons. The human quality is only an emanation that one senses at the first contact. It is revealed in his soft voice, his childlike humor, the warmth of his address, and the Viennese twinkle in his eyes. He has always stressed the necessity of clinical correlation with morbid anatomy. For him, disease is not merely a compound of chemical, molecular, physical and cellular units, but a biological change whose ultimate goal for study is healing. In this respect he is a product of

the Viennese school of pathological anatomy whose founder and guiding spirit was Rokitsansky who said "I have pursued the study of pathological anatomy as a science fertilizing clinical medicine." The spirit is expressed in the familiar Latin quotation over the entrance to the department of anatomy in the University of Vienna through which Klemperer must have often passed. "*Hic locus est ubi mors gaudet succerrere vitae.* (Here is where death rejoices to help the living.)" The nearer pathological anatomy approaches the care and understanding of the sick, the more precious it becomes.

The sense of dynamic values in the study of pathology has instilled in Klemperer a strong sense of continuity with the past and one of his later major interests has been the study of the ideologies upon which the science of pathological anatomy is founded.

No appreciation of Klemperer can be complete without an estimate of him as a teacher. His writings and his clear, fluent, logical presentations, flavored with a broad scholarship, surely have enriched the world's lore. Like Ulysses who proclaimed "I am a part of all that I have met" there is something of Paul Klemperer in all of us. But this is only a lesser part of his pedagogy. More lasting is the training of his "boys" as he calls them, even though some are of the opposite sex. Generations of residents and volunteers have passed through his laboratory and of all his manifold and pressing duties, Klemperer has always maintained that his sessions with his boys are paramount. Each autopsy is reviewed meticulously with the assigned resident and to witness the close fatherly communion between teacher and pupil, both in the laboratory and in his own home, instills a sense of envy to those not so privileged. There is something that is more spiritual that Klemperer imparts, namely a passion for pathology as a science, his wonder and curiosity. It comes as no surprise, therefore, that he has founded a school of his own whose alumni without distinction of creed, color or nationality, are scattered as Chiefs of laboratories throughout the world.

No more compact or devoted band of pupils exist anywhere. They keep in constant touch with the "Chief" not only to tap his learning, but also to obtain his counsel, and no advice is given more dispassionately. When all the tumult and shouting have ceased, it will be these that will pass on the teachings and spirit of the founder.

In this sheaf of our writings, in which this appreciation serves merely as an overture, we are only giving back to Paul Klemperer a little of what he has given us. We owe him much and our obligation can never be fully repaid.

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THE ROLE OF THE GROUND SUBSTANCE IN ATHEROGENESIS¹

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Alteration of the ground substance in atherogenesis was described by Virchow over 100 years ago. He depicted the development of endarteritis deformans, a term used by him for atherosclerosis, as hyperplasia of the ground substance. Virchow stressed the mucoid character of the thickened layers and suggested that the alteration of the connective tissue was caused by an imbibition of the intercellular substances with components of the circulating blood (1).

Experimental investigation in this field has been greatly influenced by the work of Anitschkow who experimentally produced atherosclerosis in the rabbit by cholesterol feeding (2). Elevation of serum cholesterol as well as the duration of hypercholesteremia appeared to be the factors determining experimental atherosclerosis. Some doubts concerning the validity of this concept arose when Duff and his associates observed, despite high serum cholesterol levels, inhibition of atherogenesis in alloxan diabetic cholesterol-fed rabbits (3). With the advent of corticotropin and the cortisones it was noted that the administration of these hormones in large doses elevated serum lipids (4). Contrary to expectations several groups of investigators observed independently that administration of corticosteroids to cholesterol-fed animals resulted in retardation of experimental atherosclerosis despite additional increase in serum cholesterol levels (5-7). Similar results were obtained in cholesterol-fed rabbits receiving detergents such as Tween 80 or Triton X20 (8, 9). These observations suggested that in addition to the extent and duration of hypercholesteremia other unknown factors affected decidedly atherogenesis.

Analysis of other facets of serum lipid changes such as the phospholipid-cholesterol ratio (10), elevation of triglycerides (6) or "giant molecules" determined by the ultracentrifuge method (11) did not offer a satisfactory explanation. It appeared to us that a study of the tissues in which lipid deposition takes place was warranted, especially since Klemperer re-emphasized the importance of the classical Virchowian concepts of atherosclerosis (12). Observations concerning the role of the tissue factor in atherogenesis will be presented.

CORTICOSTEROIDS, PLASMA LIPIDS AND ATHEROSCLEROSIS

The administration of corticosteroids to rabbits produced lactescence of plasma and elevations of all lipid fractions (5, 7, 13, 14). The elevation of total lipids and triglycerides was more pronounced than that of cholesterol and phospholipids. Prednisone administration was more effective than that of cortisone or hydrocortisone (Table I).

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TABLE I

Effect of cortisone, hydrocortisone and prednisone on the plasma lipid partitions of the rabbit

Corticosteroids	Daily Dose mg	No. of Animals	0			10 Days			20 Days			30 Days		
			Chol/T/E	PL	TL	Chol T/E	PL	TL	Chol T/E	PL	TL	Chol T/E	PL	TL
Cortisone.....	3.75	12	55/41	112	306	59/37	154	655	69/29	212	1090	75/45	181	822
Hydrocortisone .	3.75	11	47/35	103	505	42/25	127	771	49/25	151	745	79/41	250	1014
Prednisone.....	3.75	12	50/35	105	350	56/33	178	701	86/40	238	1260	130/46	323	2056

Chol. T/E = Cholesterol Total/Esterified
PL = Phospholipids
TL = Total lipids
All values are expressed in mg/100 ml.
(From Wang, Bossak and Adlersberg, J. Clin. Endocr. & Metab., 15: 1308, 1955)

TABLE II

Effect of cholesterol feeding and cortisone administration on plasma lipids of fourteen rabbits

	Regular Purina Chow	Cholesterol-supplemented chow	Cholesterol + cortisone, 3.75 mg/day	Cholesterol-supplemented chow
Duration, days.....	0	70	60	20
Total Cholesterol, mg%.....	50	862	2237	1093
Free Cholesterol, mg%.....	15.	241	572	325
Esterified Cholesterol, mg%.....	35	621	1665	768
Phospholipids, mg%.....	105	403	826	475
Phospholipid: Cholesterol ratio.....	2.1	0.47	0.37	0.44
Total Lipids, mg%.....	350	2053	5075	2533

In cholesterol-fed animals the intramuscular administration of corticosteroids markedly augmented the elevation of plasma lipids (Table II). Cortisone and hydrocortisone were more effective in this respect than corticotropin. Figure 1 depicts the changes in plasma lipids seen in an animal given cholesterol supplemented food without hormone administration, while Figure 2 illustrates the effect of the hormones on plasma lipids in a cholesterol-fed animal.

Gross atheromatous lesions in the aorta were generally observed after one month of cholesterol feeding (1 gm. per day). Early lesions assumed the form of tiny sandy granules mostly over the ascending part and the arch of the aorta, especially around the orifice of the innominate artery. With continued cholesterol feeding the atheromatous plaques became larger and more numerous (Figures 3, 4). Some atheromatous lesions were seen as thin, but definitely demarcated streaks with longitudinal orientation, others became confluent and formed irregular plaques. The lesions then extended to the thoracic and abdominal aorta, originating at the orifices of the branching arteries. Similar changes were observed in the pulmonary arteries. The cusps of the mitral or aortic valves were not infrequently thickened by thin and tiny plaques of atheroma.

After three to four months of cholesterol feeding more extensive atherosclerosis was observed. Large, thick and confluent plaques covered the ascending and

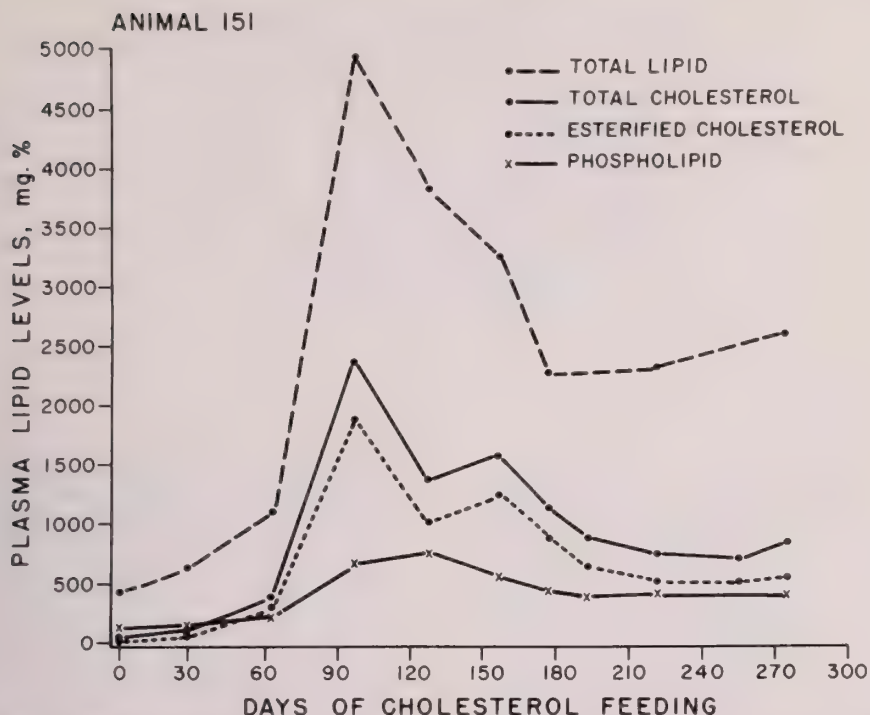


FIG. 1. Plasma lipid fractions of Rabbit 151 fed cholesterol-supplemented chow for 285 days. Note steady increase of all lipid fractions during 90-120 days, moderate decrease thereafter and stabilization at lower levels after 180 days.

descending aorta. There was considerable thickening and atheromatosis of the mitral and/or aortic valves, and of the coronary and pulmonary arteries. Lipidosis of kidneys and spleen was usually present. As will be discussed later, some animals showed xanthomata of the skin and joints.

Animals injected with cortisone or hydrocortisone in addition to cholesterol feeding exhibited, in comparison with animals receiving cholesterol supplements alone, milder degrees of atherosclerosis, despite higher plasma lipid levels (Figures 5a & b). The atheromatous lesions in the hormone-treated animals were less extensive and less confluent, were smaller and thinner, and only rarely involved the descending aorta. Similarly, the changes in the pulmonary artery and in the mitral or aortic valves were of a milder degree. In some of these animals practically no atheromatous lesions were observed after 45 days of the experiment (Table III). Figures 5a & b illustrate the aortic lesions seen in the two groups of animals after comparable periods of cholesterol feeding.

EFFECT OF CORTICOSTEROIDS ON TISSUE PERMEABILITY

That corticosteroids inhibit the effect of hyaluronidase on capillar permeability has been demonstrated by Benditt *et al.* (15). Seifter *et al.* (16) noted enhancement of atherogenesis in cholesterol-fed rabbits injected with hyaluronidase,

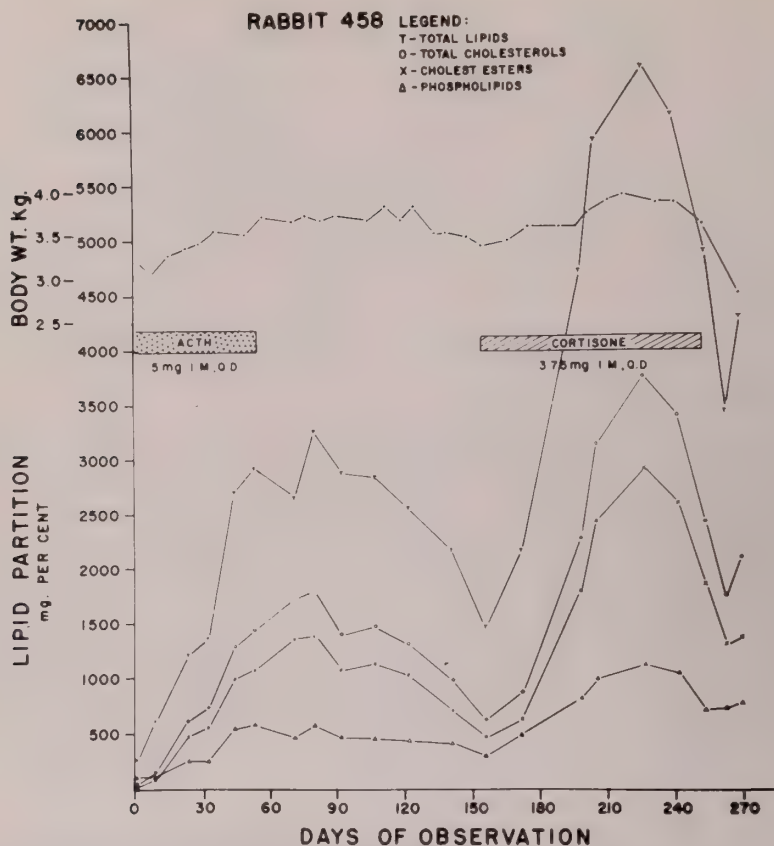


FIG. 2. Changes in plasma lipids in Rabbit 458 fed cholesterol-supplemented chow for 270 days. Adrenocorticotropin, 5 u., was injected daily intramuscularly for the first 60 days (1st course). Cortisone in doses of 3.75 mg. daily was given for 100 days (second course). Note slight superimposed elevation of all plasma lipids during Course I and marked elevation during Course II.

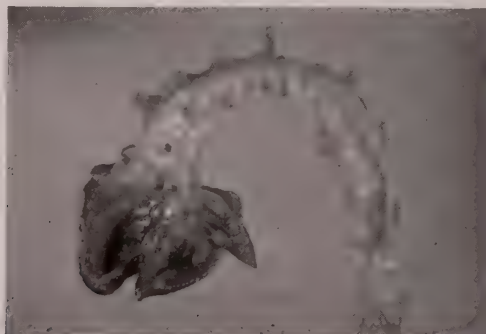


FIG. 3. Heart and aorta of Rabbit 362 on cholesterol-supplemented chow for 71 days. Note irregularly shaped atheromatous plaques over the ascending aorta, especially around the orifice of innominate artery and small granular atheromatous plaques over the arch of the aorta. The descending and abdominal aorta was free from intimal lesions. Thin plaques of lipid deposition are present over the mitral valves.

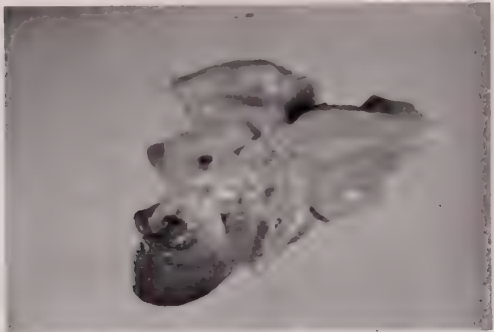


FIG. 4. Same animal as in Fig. 3. Note large atheromatous plaques in the pulmonary artery and beginning of atheroma formation over the orifices of the branching arteries in the right lung.

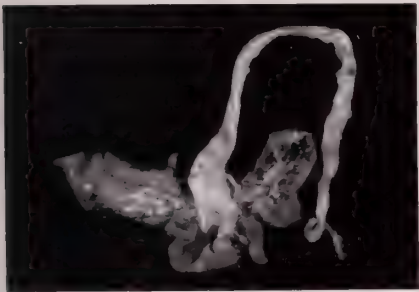


FIG. 5a.

FIG. 5a. Extensive atheroma formation over the aorta, pulmonary arteries, aortic and mitral valves of Rabbit 520 fed cholesterol-supplemented chow for 5 months. The entire intimal surface of the aorta is covered by plaques of atheroma. Plasma lipid levels at the time of sacrifice were: Cholesterol, total 896, esterified 648, phospholipids 382 and total lipids 2180 mg. %.

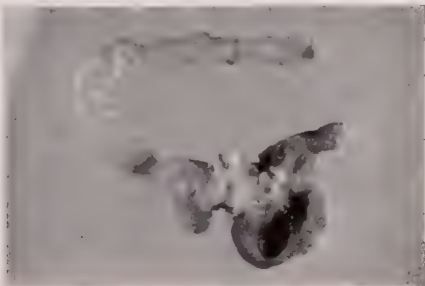


FIG. 5b.

FIG. 5b. Rabbit 384 was on cholesterol-supplemented chow for 5 months. Cortisone, 5 mg. intramuscularly daily, was given during the 3rd and the 4th months of cholesterol feeding. Highest plasma lipids during this period were: Cholesterol, total 2860, esterified 2108, phospholipids 1268 and total lipids 8040 mg%. (The plasma lipid levels at the time of sacrifice were: cholesterol, total 756, esterified 564, phospholipids 320 and total lipids 1810 mg%). Note moderate degree of atheromatosis over the heart and aorta comparable with lesions seen in animals fed cholesterol-supplemented chow for two months (Compare this figure with Figures 3 and 5a).

TABLE III

Effect of hormone injection on the development of atherosclerosis in cholesterol-fed rabbits

(Duration of Experiment: 8 weeks)

Procedure	Ascending Aorta	Descending Aorta	Pulmonary Arteries	Mitral and/or Aortic Valves
Chol. feeding.....	++	+	++	+
Chol. feeding + Cortisone.....	±-+	±	+	0-±
Chol. feeding + Hydrocortisone.....	±-+	±	+	0-±

(From Wang, Schaefer and Adlersberg, Endocrinology 56: 628, 1955)

TABLE IV

Atheroma formation in four groups of cholesterol fed animals under various experimental regimens

Group	No. of Animals	Additional Treatment*	Degree of Atherosclerosis	
			Aorta	Pulm. Art.
A	9	None	1.2	0.9
B	5	Cortisone 3.75 mg daily	0.5	0.4
C	13	Hyaluronidase, 1000 TRU and cortisone 3.75 mg daily	1.5	0.6
D	14	Hyaluronidase 1000 TRU daily	2.0	1.8

* Cholesterol feeding was continued for 8 weeks. Additional treatments were given during the last four weeks of cholesterol feeding.

(In part, from Wang, Schaefer and Adlersberg, *Circulation Research* 3: 293, 1955)

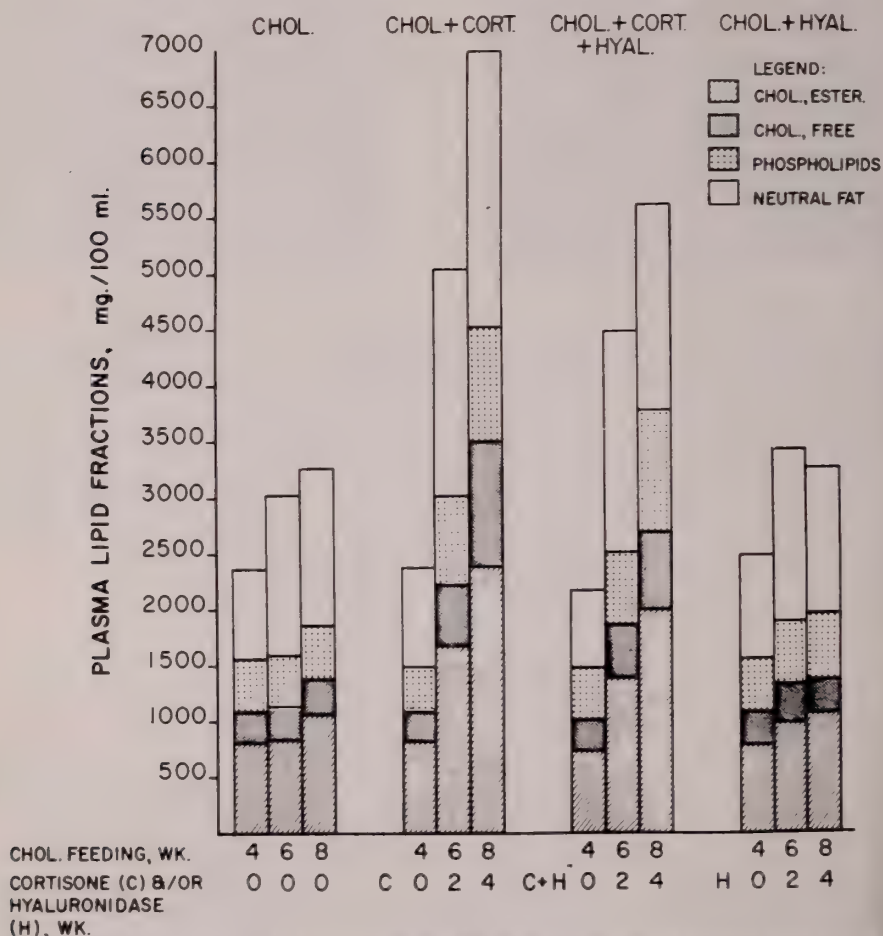


FIG. 6. Effect of cortisone and/or hyaluronidase administration on plasma lipid levels in 4 groups of cholesterol-fed animals. For details, see text.

despite lower plasma cholesterol levels. This observation was explained by increased rate of cholesterol deposition in the tissues.

The influence of corticosteroids and hyaluronidase on atherogenesis was observed in four groups of animals (A-D) (17). In all four groups the animals received cholesterol-supplemented chow for eight weeks with a daily intake of cholesterol of approximately 1 gm per day. After four weeks of cholesterol feeding the animals of group A continued to receive cholesterol alone; those of group B were injected daily with 5 mg cortisone acetate intramuscularly, those of group C were injected daily with both 5 mg cortisone-acetate and 1000 turbidity reducing units (TRU) hyaluronidase; and those of group D were injected with 1000 TRU hyaluronidase daily. The changes of the various plasma lipid fractions in these groups of animals after four, six and eight weeks of cholesterol feeding, before cortisone and or hyaluronidase administration as well as two and four weeks thereafter are shown in Figure 6.

After four weeks of cholesterol feeding, there were marked elevations of plasma total and esterified cholesterol, phospholipids and total lipids. Continuation of cholesterol feeding alone for a total of six and eight weeks (group A) produced slight additional elevations of all plasma lipid fractions. Cortisone injections added to cholesterol supplements resulted in marked superimposed elevations of all plasma lipid fractions (group B). The combined administration of cortisone and hyaluronidase to cholesterol-fed animals (group C) resulted in elevations of

CHOLESTEROL FEEDING

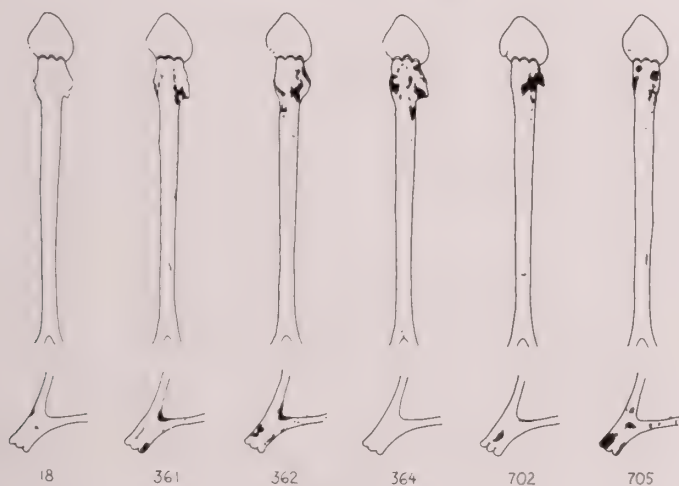


FIG. 7a.

Fig. 7. Comparison of atheroma formation in the aorta and pulmonary arteries in 3 groups of animals fed cholesterol for 2 months. 7a—Cholesterol feeding alone. 7b—Cortisone, 5 mg. daily, was injected daily during the 2nd month of cholesterol feeding. 7c—Hyaluronidase, 1000 TRU daily, was injected daily during the 2nd month of cholesterol feeding. In each figure, the upper drawings represent the heart and aorta and the lower the pulmonary artery. Note moderate atheromatous lesions in the aorta and pulmonary arteries in the control group (7a), thinner and less extensive lesions in the hormone-injected group (7b) and more extensive lesions in the enzyme-injected animals (7c).

CHOLESTEROL + CORTISONE

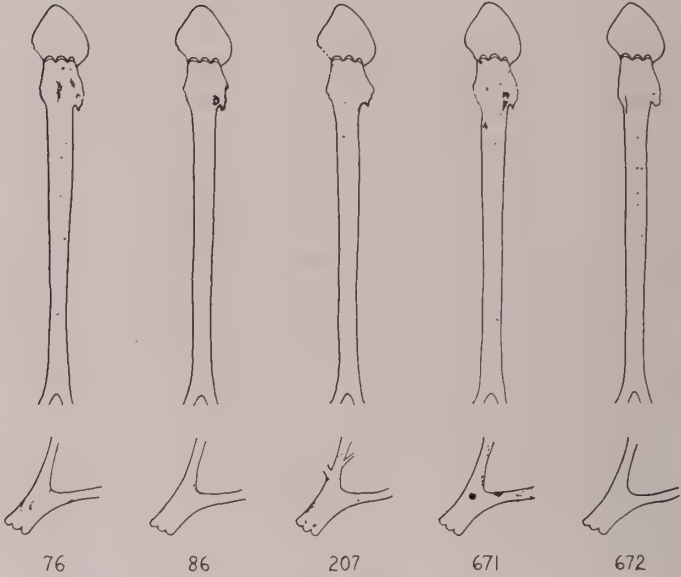


FIG. 7b.

CHOLESTEROL + HYALURONIDASE

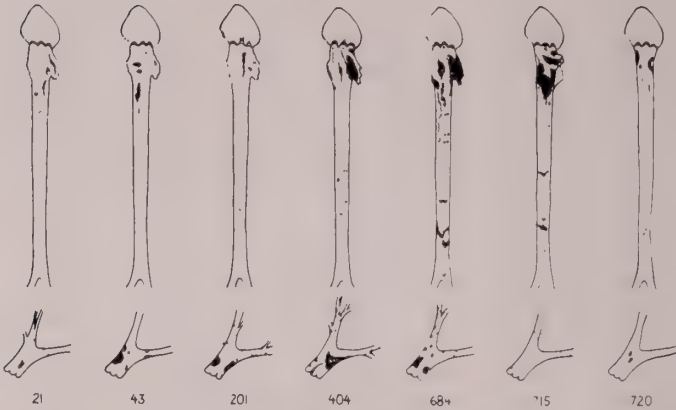


FIG. 7c.

plasma lipid fractions on a lower level than those seen in group B. Hyaluronidase alone combined with cholesterol supplements (group D) produced no significant changes in plasma lipids when compared with group A. Thus the effect of cortisone on plasma lipids was counteracted by the simultaneous administration of hyaluronidase.

Atheroma formation in the aorta and pulmonary arteries of the animals under the various experimental conditions is depicted in Figures 7a-c. The atheroma-



FIG. 8. Paws of a rabbit, 384, fed cholesterol-supplemented chow for 160 days. Note small cutaneous xanthoma of the toe with beginning ulceration in the center (arrow) and thickening and cracking of the sole of foot (arrow).

tous lesions after two months of cholesterol feeding alone are shown in Figure 7a. Animals given hyaluronidase exhibited the most extensive atheromatous lesions (Figure 7c) in contrast to animals given cortisone which exhibited the least pronounced changes (Figure 7b). One may reason that hyaluronidase enhanced atheroma formation by increasing permeability of the connective tissue; this mechanism was counteracted by cortisone. It appears then that factors affecting the ground substance of the arterial wall have an important role in the deposition of lipids.

EXPERIMENTAL XANTHOMATOSIS IN THE RABBIT

The deposition of cholesterol in the skin, joints and bones in cholesterol-fed animals offered an opportunity for the study of the relationship between changes in the connective tissue ground substance and deposition of lipids in these organs.

A group of 120 male rabbits fed cholesterol-treated purina chow for periods varying from two weeks to one year were used for this study (18). A small number of animals (2.5 per cent) exhibit cutaneous xanthomatous lesions after two to three months of cholesterol feeding. After three to six months, 21 per cent of the animals, after six to nine months, 50 per cent and after nine to twelve months, 100 per cent of the animals showed xanthomata of the skin.

These lesions were noted first on the paws, as small reddish-yellow nodules, 1-3 mm. in diameter, between the toes and over the heels. The size of the nodules slowly increased to a diameter of 1-1.5 cm (Figure 8). The skin of the soles became thickened and cracked. In some of the animals, elevated yellowish tophi,



FIG. 9. Roentgenologic appearance of the left hind leg of Rabbit 171 after 180 days of cholesterol feeding. Note thinning of the cortex with fan-shaped widening and osteosclerotic changes in the lower end of the tibia and in the tarsal bones resulting in complete destruction of the ankle joint. Also notice periosteal elevation and soft tissue swelling. Small nodular xanthomas were noted after 3 months of cholesterol feeding. (17).

1-3 mm. in diameter, were seen scattered over the ears. Preceding traumatic injury to the ear, e.g., at the sites of puncture for blood sampling, usually predisposed the skin to the development of xanthomatous nodules. In many instances, ulceration of the large xanthomata and secondary infection with abscess formation complicated the picture. The skin over the back and neck appeared generally thickened (hyperkeratosis). Loss of hair was frequently observed.

A typical well-developed xanthomatous skin nodule was characterized histologically by thinning of the epidermis, marked distention of the dermis with fat-laden foam cells and a central pool consisting of cholesterol crystals and cellular debris.

Thickening and swelling of the ankles and knee joints was generally noted in animals fed cholesterol for more than six months. The firmness of the swelling suggested deposition of cholesterol in these tissues. Serial roentgenologic studies were used to demonstrate the changes in the bones and joints. Considerable thinning of the cortex of the long bones was noticed after three to five months of cholesterol feeding. Osteosclerotic changes and destruction of the joints were found when marked xanthomatous lesions of the bones and joints were present (Figure 9). Pathologic fractures were often seen.

Microscopically the deposition of foam cells was found in the synovial membrane, periosteum and bone marrow after two months of cholesterol feeding. In advanced stages large numbers of foam cells and cholesterol crystals were very

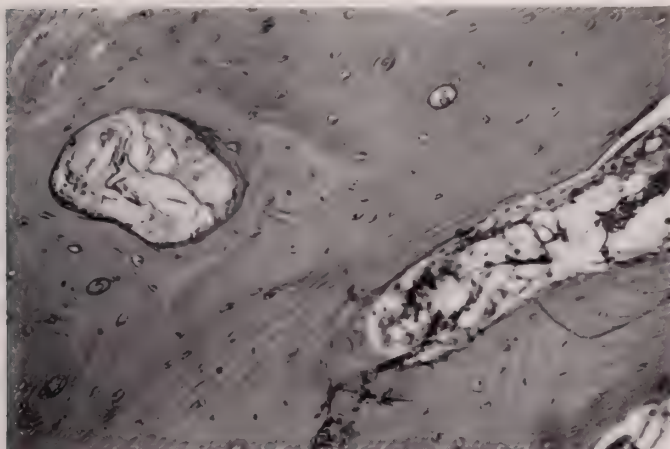


FIG. 10. Clusters of foam cells and of cholesterol crystals in Howship's lacuna of the femoral cortex of animal, 458, sacrificed after 270 days of cholesterol feeding ($\times 400$ Hematoxylin-Eosin stain).

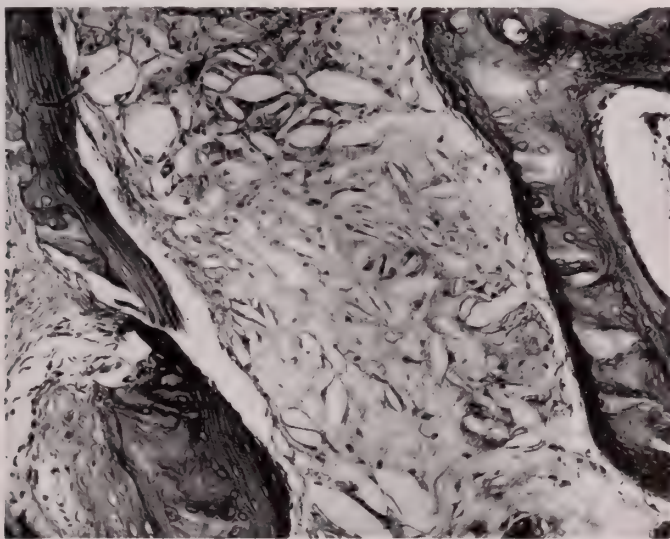


FIG. 11. Collection of large numbers of foam cells and cholesterol crystals at site of fracture of the lower end of femur. This animal, 502, was fed cholesterol for $21\frac{1}{2}$ months. ($\times 120$ Hematoxylin-Eosin stain).

frequently observed in the bone lacunae (Figure 10). The deposition of lipids became more prominent when pathological fracture was present (Figure 11).

ALTERATION OF GROUND SUBSTANCE AND LIPID DEPOSITION

Cutaneous xanthoma not visible to the naked eye but detectable by microscopic examination could be demonstrated rather early. Isolated foam cells or nests of them were found in the perivascular and perineural spaces in the corium after 20 days of cholesterol feeding. They were usually accompanied by a local

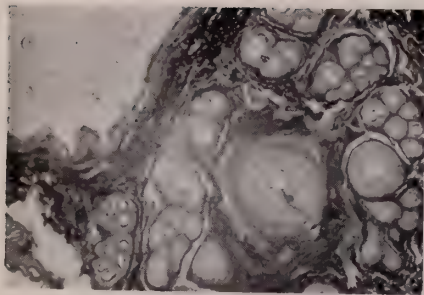


FIG. 12a.



FIG. 12b.

FIG. 12a. Skin of control rabbit. Acid mucopolysaccharides (AMP) are seen only in the connective tissue around the hair follicles (Rinehart's modification of Hale's colloidal iron stain, $\times 36$). (In the kodachrome which cannot be reproduced the connective tissue around the hair follicles displayed blue color).

FIG. 12b. Skin of Rabbit 388 fed cholesterol for 30 days. Note marked increase of acid mucopolysaccharides in the corium (Rinehart's modification of Hale's colloidal iron stain, $\times 36$).

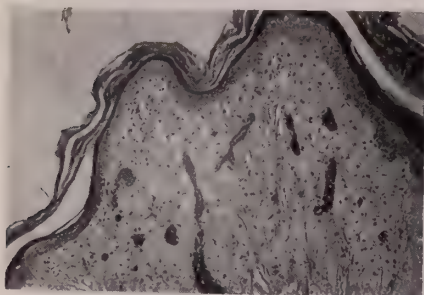


FIG. 13a.

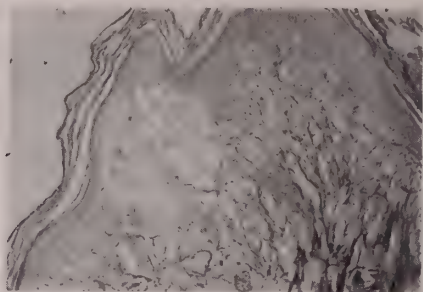


FIG. 13b.

FIG. 13a. Skin of Rabbit 151 fed cholesterol for $9\frac{1}{2}$ months. Note infiltration of skin with large numbers of foam cells and numerous clefts of cholesterol crystals (Hematoxylin-Eosin $\times 36$) (18).

FIG. 13b. Same section as 13a. Note almost complete absence of AMP (Rinehart's modification of Hale's colloidal iron stain, $\times 36$).

bluish-violet hue of the ground substance in sections stained with hematoxylin-eosin. This change in tingibility probably reflected a qualitative and/or quantitative alteration of the connective tissue ground substance.

Further studies with a special stain revealed rapid accumulation of acid mucopolysaccharides in the dermis in cholesterol-fed rabbits (19). The increase in acid mucopolysaccharides in the connective tissue was demonstrated by the Rinehart and Abul-Haj's modification of the colloidal iron technique of Hale (20). It was most striking in the early stages of lipid deposition (Figures 12a & b). With advancing xanthomatosis of the skin and greatly increased lipid deposition, the Prussian Blue reaction of the tissue was decidedly diminished in comparison with the earlier stages (Figures 13a & b). The reduced intensity of Prussian Blue reaction may reflect an actual reduction of the quantity of acid mucopolysaccharides in the connective tissue or it may represent a qualitative alteration of the ground substance. Craig has found that, in Gaucher's disease, the presence of lipids in the tissues inhibited their reaction to colloidal iron (21). In the light

of this observation, a mild Prussian Blue reaction seen in advanced cutaneous xanthoma of the cholesterol-fed rabbit also may be due to the deposition of large amounts of lipids.

In the joints of untreated animals abundant quantities of acid mucopolysaccharides were demonstrated in the cartilaginous tissue, the ligaments and the tendons. No further increase of acid mucopolysaccharides or deposition of foam cells was found in these tissues after cholesterol feeding. As stated previously, foam cell deposition in the bones and joints was limited to the periosteum, Howship's lacunae, bone marrow, synovial membranes and the fibrous sheaths of tendons or ligaments. The relationship between acid mucopolysaccharides of the ground substance and the deposition of the lipids was obscure. The original amounts of acid mucopolysaccharides in various organs had no bearing on the subsequent lipid deposition after cholesterol feeding. Factors such as blood supply, lymphatic drainage and fibroblastic activity offered partial explanation only. It has been known that the chemical composition of acid mucopolysaccharides in the ground substance differs in various connective tissues (22). One may speculate that these differences in composition may result in different affinity to lipids and thus influence lipid deposition.

SUMMARY

1. The administration of the cortisones to cholesterol-fed rabbits resulted in superimposed elevations of all lipid fractions. Despite the elevation of all lipid fractions the cholesterol-fed hormone-injected animals exhibited less atherosclerosis than those fed cholesterol alone. This suggests that in addition to the concentration of plasma cholesterol and duration of hypercholesteremia some other factors obscure at present play an important role in atherogenesis.

2. The additional elevation of plasma cholesterol and the inhibition of atherogenesis produced by cortisone administration in cholesterol-fed rabbits were counteracted by the simultaneous administration of hyaluronidase. The retardation of atherogenesis in cortisone-treated cholesterol-fed animals could be explained by diminished tissue permeability for lipids.

3. Experimental production of xanthomatosis in skin, bone and joints offered an opportunity to study the alterations of the connective tissue ground substance in relation to lipid deposition. Rapid accumulation of acid mucopolysaccharides in the corium was seen in early xanthomatosis. In advanced xanthomatosis with increased lipid deposition in the tissue the amount of acid mucopolysaccharides in the ground substance was diminished. The relationship between acid mucopolysaccharides of the ground substance and lipid deposition in the tissues was discussed.

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A CONCEPT OF THE ORIGIN OF THE CARDIAC VALVULAR VEGETATION*

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INTRODUCTION

It is especially fitting that this presentation appear in the Festschrift to honor Dr. Paul Klemperer, for this study represents a direct application of his pioneer and fundamental work on collagen over these many years.

Some years ago, MacNeal *et al* (1), produced endocarditis in the rabbit by repeated intravenous injections of large quantities of living *Streptococcus viridans*. They claimed the lesion was occasioned by initial localization of the organisms on the endothelium of the valve. However, the lesion might result from a non-bacterial, non-specific reactive change in the valve substance. The production of endocarditis by Dietrich (2) using serum and dead enterococci, by Hawn and Janeway (3) using crystalline albumin and gamma globulin, by Moore and Wauch (4) using massive doses of globulin in rabbits, and by Strehler (5) using anti-aorta antisera, seem to indicate a non-bacterial mechanism.

On this basis an attempt was made to reproduce the lesions following the technique of MacNeal *et al* (1), dead bacterial cultures of *Streptococcus fecalis* were injected into rabbits in place of live organisms. Non-bacterial vegetations were produced. We have produced lesions of non-bacterial thrombotic endocarditis (NBTE) experimentally in animals in order to clarify their pathogenesis and to study their histological, chemical and ultramicroscopic nature. This has been done in a variety of ways: in the rabbit, by intravenous inoculations of dead bacterial broth cultures; in the rat, repeated tumbling of the animal, exposure to cold, exposure to simulated high altitude, exposure to high and low oxygen tension. The detailed results of these experiments will be reported elsewhere.

The earliest macroscopic change in the experimental lesion is a localized translucent swelling of the valve in focal nodular zones resembling "edema" with a tendency to distribution along the line of closure. Small foci of opacity appear in the areas. Microscopically, the early changes in the valve collagen shows vacuolization of the ground substance, an increase of eosinophilic staining and a hygroscopic swelling. The localized edema of the valve, particularly along the line of closure and adjacent chordae tendinae, merits greater emphasis. Frequent recurrence compensates for the lack of dramatic character of the "edema" change. It has been discounted unduly, because it is a common autopsy finding. This change is seen in the experimental animal before vegetations appear.

With loss of the overlying endothelium of the valve surface, altered valve sub-

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stance and precipitated blood proteins appear above the surface and NBTE follows. Moore (6) considered "necrotic" valve substance an important element of the vegetation. Allen (7) maintained that a good portion of the endocarditis vegetation was not thrombotic, but consisted of altered protuberant underlying collagen. It may be recalled that gelatin is altered collagen and is notable for the large quantities of water it can absorb, with attendant marked swelling. Similarly, glue is altered collagen, and an early thrombotic vegetation can possess a tacky quality. Blood cells, protein and bacteria might be expected to be readily included. Both the "edema" change and the evolved vegetation participate in the production of valve distortions, chronic and acute.

The experiments indicate the mechanism of bacterial localization. Positive blood cultures were obtained in some of our rabbits first infected with dead bacteria for two weeks to produce NBTE five days after a single injection of living organisms. Ordinarily blood cultures are sterile soon after a single intravenous inoculation in rabbits, and remain sterile. Organisms were found on the surface of the vegetation in three valves.

Klemperer *et al* (8) found that four of twelve cases of Libman-Sacks endocarditis showed surface bacterial growth. Continued growth of such bacterial "contaminants" leads to local exudative inflammation and destructive proteolytic reaction. The severe form of acute vegetative and ulcerative lesions follows, or the classical subacute bacterial endocarditis, depending on the virulence, the nature of the organism and general immunity factors, as suggested long ago by Schottmuller, Osler, Ligman and others.

THEORETICAL CONSIDERATIONS

All vegetations seem to be initially NBTE, derived in part from the valve proper, either of the ground substance or of the collagen, plus precipitated blood protein. They may then include some thrombotic elements and may become contaminated with bacteria to yield the classical bacterial vegetation. The unorthodox viewpoint of an underlying metabolic cause is supported by the production of valve lesions in scorbutic guinea pigs by Rinehart, (9) by the hypertrophy of the adrenals in experimental endocarditis by A-V shunts by Lillehei *et al*, (10) by other forms of stress cited with endocarditis, and by the dramatic effect of adrenal hormones on connective tissue in inflammation, wound healing and their therapeutic benefits on diseases associated with endocarditis; all would seem to implicate the "pituitary-adrenal axis". Endocarditis was seen in adrenalectomized rats. The endocrine system plays an important part in the production of the valve lesion, as well as its form and its rate of resolution and healing; these effects are probably mediated through enzymatic controls of connective tissue metabolism.

The NBTE vegetation can pursue a variable course with a range of cytological and histological reaction. The rheumatoid-like nodule of the calcified sclerotic aged valve, the rheumatic verrucae and the lesion of endocardiosis represent graded morphological reactions. Each final pathological picture is an expression of the graded response to the precipitated protein of the primary vegetation.

Initially there is no cellular reaction or inflammatory change. The cellular reaction occurs subsequently and will vary in character and with duration. It is usually minimal if uninfected. Oriented cellular palisading might be expected about altered larger "indigestible" macromolecules of protein, nucleoprotein and lipoglycoprotein moieties which persist and are not further depolymerized and degraded. Instead of ordinary lysis with complete absorption, the macromolecules give rise to the primitive cellular reaction of Metchnikoff with delimitation and organization, i.e., a corresponding intra-cytological equivalent to submicroscopic moieties, of a granulomatous foreign body histological reaction. This basic abnormality may well be an exaggeration or a variant of the type of biochemical mechanism that is the fundamental cause of arteriosclerosis at the very earliest morphological initiation of this degenerative process. The hemotoxylin bodies of lupus erythematosus, Klemperer *et al*, (11), and the L.E. cell, Lee *et al*, (12) may be considered equivalent cytological reactions to enzymatically altered nucleoprotein. Some changes in and on the valve are then the equivalent of the slow carnification of an organizing pneumonia, in contrast to the rapid liquefaction and absorption characteristic of the usual exudative pneumonitis.

The rheumatic-like verrucae produced by Selye (13), the rheumatic lesions of Rich *et al* (14), and the endocardial lesions found by Winternitz (15), with crude kidney extracts injected intravenously, can be explained by this broader concept. Similarly, the vegetations produced with pitressin may be cited, and the heretofore inexplicable cardiac lesions with carcinoid tumors including the fibrous distortions and the NBTE noted by Spain (16).

Clawson (17), Murphy (18), Thomas (19), Stetson (20) and others produced lesions of the endocardium and of the valve by sensitization and the application of the Arthus and the Schwartzman phenomena. Some have thought the changes in the valve to be a result of organ sensitivity, or an allergic manifestation. Polysaccharide and protein antigen penetration into connective tissue, and persistence there longer than in other tissues, demonstrated by Coons (21), is significant on this score. No evidence of skin hypersensitivity was seen in our rabbits. The production of endocarditis in rats subjected to high altitude by Highman and Altland (22), is noteworthy; surely it is not an allergic or sensitivity reaction. A mechanism of sensitivity or allergy does not apply to the endocarditis found in natural or in experimental A-V shunts of Lillehei *et al* (10), nor to other forms of non-specific stress, as tumbling, high altitude, cold, or the low or high oxygen tension at normal atmospheric pressure.

SIGNIFICANCE OF THE FRESH LESION AND ITS SECONDARY CHANGES

NBTE is asymptomatic. Distortion of the valve by healing and calcification of NBTE yield later manifestations, without immediate clinical features. The uninfected NBTE adds no new symptoms to the underlying primary disease entity. The symptoms of embolism, its most dramatic complication, are often lost in the underlying disease process. NBTE is often a "terminal" lesion because it is usually associated with grave, lethal entities that initiate the final metabolic fault causing NBTE in the terminal stages of the disease process. Disease entities fre-

quently associated with NBTE, as uremia, malignancy, and nutritional deficiency in a broad sense, produce their toxic and metabolic disturbance to a maximal degree just before the death of the patient. One would expect to find the resulting NBTE at autopsy in an early phase of its evolution, having been initiated only a short time before death. For this reason, NBTE has been discounted as a pathological curiosity of little clinical or pathological significance.

If recovery from the associated disease occurs, and the vegetation is no longer "terminal", then the vegetation undergoes absorption or slow alteration, fibrosis and/or calcification. The healing process renders the valve prone to repeated similar alterations and can yield final marked distortions of the valve. The secondary changes in the interstitial tissue and vegetation are additive. The "edema" change or NBTE lesions recur with the many forms of stress the organism is heir to; they may resolve incompletely and add increments of fibrous tissue, incorporating the chordae in the valve and yielding a fusion of the cusps (stenosis) and an elongated fibrous thickening (billowing-sail distortion). Any persistent distortion found long after is ordinarily considered a "degenerative sclerotic process." This is a form of arteriosclerosis in a fundamental sense, if NBTE is considered an exaggerated local form of arteriosclerosis.

Complete absorption of an NBTE lesion can and does occur. When the vegetation contains an abundance of fibrin, more or less complete absorption can be expected by fibrinolysis and efficient fibroblastic scarring. It is fibroblastic organization of NBTE which yield aortic cusp "whiskers" or Lambl's excrescences and bridging fibrous tabs at the commissures.

In the absence of absorption or infection, a fibrous thickening or calcification of the valves occurs. Gradations from the earliest "terminal" type of vegetation without any reaction, to the different healing phases with varying degrees of absorption and collagenous transformation, with or without reactive inflammatory changes, are seen frequently. Allen and Sirota (23), classified the NBTE vegetations microscopically as degenerative, exudative and healed. Transitional microscopic features among NBTE renders the classification of instances of some duration difficult. Instances of vegetations with surface bacterial infection, and others showing the appearance of transition to acute or subacute bacterial endocarditis, have been found. During some of the stages of healing with a sluggish cytological reaction, NBTE resembles the histology of rheumatic verrucae or the atypical verrucous vegetations. Allen and Sirota (23) note that "some of the verrucae of Libman-Sacks disease may be indistinguishable from those of degenerative endocardiosis." Histological similarity of some of the bland vegetations to rheumatic lesions was indicated by Jaffee (24), Figs. 1 and 2.

When NBTE vegetations contain an abundance of altered degenerative collagen, calcification predominates and the original contour and shape may be preserved in the calcified state. A healed "embalmed", sterilized bacterial vegetation can account for only a rare instance of calcified cusp lesion. This pathologic calcific distortion of the aortic valve is too common for this sole mechanism. Calcification in and on valves is common, and gross protuberant calcific masses showing transitions to NBTE are seen often. Calcification is uncommon in any

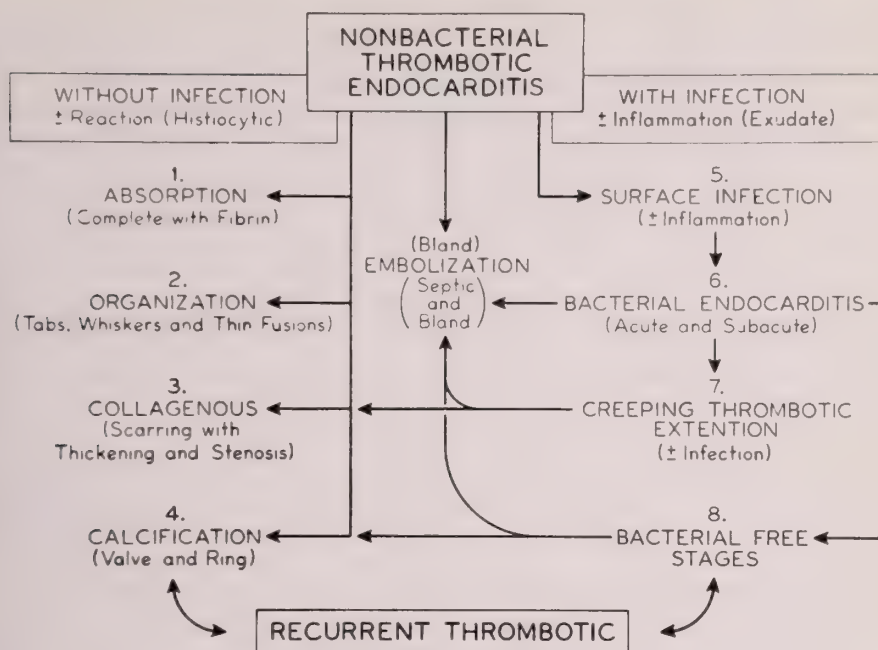


FIGURE 1

CLASSICAL FORMS of VEGETATIVE ENDOCARDITIS*

NON-BACTERIAL

1. THROMBOTIC
(Endocardiosis)
2. RHEUMATIC
3. ATYPICAL VERRUCOUS

BACTERIAL

4. SURFACE CONTAMINATION
of 1, 2 and 3
5. SUBACUTE
6. ACUTE

**Transitional, Intermediate, Healing and Healed Stages of all the Classical Forms have been encountered with the exception of Healed Atypical Verrucous.*

FIGURE 2

rheumatic verrucae proper. Past rheumatic fever has not been associated with many instances of calcific aortic stenosis clinically or pathologically. The microscopic finding of a few Aschoff-like cells or bodies does not stamp the entire gross valve lesion as rheumatic. As noted, other healing valvular and myocardial foci can resemble the Aschoff nodule. Are we not stretching the specificity of the microscopic picture in a Procrustean manner to fit the gross findings? Calcific stenosis can occur with valves which have thin, pliable edges and commissures, showing no evidence of other prior local involvement by rheumatic

fever, or rheumatic pathology elsewhere. Nor can rheumatism account for the fusion of two valve cusps at a single commissure, and at a point away from the valve edge, the remainder of the valve and its edges persisting unaltered.

A full-blown mitral stenosis seldom develops immediately following an attack of rheumatic fever, even if severe. It often follows a mild attack, or no history of rheumatism at all. The distortion of the valve to give stenosis is often initiated by classical rheumatic involvement, but its ultimate progression to stenosis may well represent the summation of non-specific changes in the valve, proceeding to fibrosis and calcification, independent of any additional increment of specific rheumatic activity. By this concept, the stenosis of the mitral valve, long after a single attack of rheumatic fever, can have the same mechanism as the stenotic aortic valve in the aged. The gross distortion in both may be similar and independent of rheumatism.

THE LOCALIZATION OF VEGETATIONS

The remarkable localization of all vegetations may be explained as resulting from an underlying metabolic fault of the valve substance. Collagen elsewhere is implicated in similar fashion, but this remains cryptogenic. The valves, however, are always carefully inspected, and vegetations indicate their presence in the form of changing murmurs, embolization and ready secondary bacterial infection.

Vegetations occur on the healthy, unscarred endocardium. The endocardium, and particularly the valves, possess a relative abundance of background matrix substance, prone to local stress, and to general stress through the endocrine system. This labile reactive myxomatous tissue, rich in complex, highly polymerized substances, is susceptible to hormone control. This abundant homogeneous tissue in the endocardium and in the valve, accounts for the preferential localization of vegetations in the endocardium selectively and in the valves particularly. The uniform gross and microscopic appearance and the localization of the linear rows of rheumatic verrucae along the line of closure cannot be explained as the result of chance virus embolization or concentration, or selectivity of focal allergic sensitization. The proneness to stress alteration of this region of the valve offers an explanation for this remarkable phenomenon in rheumatic fever. The distribution of the Libman-Sacks vegetations on the under surface of the valves and in endocardial pockets is irregular because their site depends upon the chance involvement of the endocardium by the widespread enzymatic disturbance beyond the valve tissue existing in lupus.

The localization of bacterial vegetations on the normal valve and on the most scarred avascular hyalin portion of a valve cannot be explained as vascular embolization. That mechanism would require identity of size of clumps of bacterial colonies or a specific local bacterial phagocytosis by the capillary or valvular endothelium. No colonies of bacteria, let alone colonies of uniform size, have been found in the blood stream. Phagocytosis of bacteria by the lining endothelium seems inadequate to explain the localization encountered on valve cusps, even though this process may occur occasionally.

Fibrotic endocardium is a very common site for an acute or subacute bacterial

endocarditis, and particularly NBTE. This constitutes one of the gravest clinical hazards of old valve lesions, whether caused by past rheumatism or congenital heart disease. If a biochemical metabolic mechanism is involved in their formation, then in general, vegetations will appear where this fundamental alteration or "devitalization" of the collagenous valve substance is most liable to occur. Vegetations would be expected where previous collagen alteration and hyalin fibrosis has occurred, i.e., the damaged valve or thickened endocardium. Scott (25) notes a similar thrombotic mechanism in regions of venous intimal thickening.

All forms of endocarditis are seen on such distorted scarred valve structures. This is particularly true now in cases of calcified aortic stenosis in the older age group. Once any valve distortion is established, the tendency is increased for additional increments of NBTE to occur and to calcify, and this is accumulative with age. The tendency to degenerative change in the collagen throughout the body is more marked in older individuals (Silberberg and Silberberg) (26). The frequency of NBTE with advancing years was noted by Wallach *et al* (27). Heberden's nodes and other degenerative lesions of the mesenchyme are frequently present.

An inverse incidence exists between the bacterial and non-bacterial lesions. Since 1944 the use of penicillin has decreased bacterial endocarditis while NBTE has increased. The incidence of all forms of endocarditis, particularly the bacterial forms, shows marked increase among the aged (with correction for age of autopsy population) (28). The aged valve has always shown the highest incidence of thrombotic vegetations, and now also shows highest incidence of bacterial vegetations too. The infective vegetations are also now more often of the acute form. Therapy is effective in youth to lower the incidence in the young. Bacterial endocarditis is more often undiagnosed and the therapy less successful in the aged, accounting for this change in the age frequency pattern.

THE PHENOMENON OF EMBOLISM

The role of NBTE in the general pathology of embolism, and in all forms of vegetative endocarditis in particular, is not sufficiently credited. NBTE is attached superficially and leaves little evidence of its site of former attachment once it is dislodged as an embolus. Detection of the exact source of such emboli requires most careful microscopic scrutiny of all minute irregularities and superficial zones lacking glistening endocardium, for a fibrin coating. These minimal changes can be found only if the valve is seen soon after the vegetation has been detached. Healing and endothelialization occur rapidly and conceal all evidence of the site of origin. Then an infarct is seen in some peripheral organ with no embolic source evident, and this experience is all too common.

The high incidence of embolism in cases of old rheumatic heart disease is a reflection of the high incidence of NBTE in such cases. Auricular thrombi, of course do cause such embolic episodes. NBTE are more friable than organizing thrombi, and more easily detached to yield emboli. Auricular thrombi show a greater tendency to organization and firmer adhesion because fibrin represents

their major constituent. This feature accounts for their remaining so long in the auricular appendage so often without embolizing. Auricular thrombi are not initiated by "local blood stasis" but rather by an underlying endocardial alteration which is the equivalent of NBTE. In contrast, NBTE on the valves is subject to the forces of shearing displacement of the main blood current. Of all vegetations, the NBTE show the least reaction. The altered collagen in their substance is less amenable to rapid fibroblastic organization, and therefore persist longer in a detachable state and are dislodged as emboli more easily and for a longer interval of their existence. This explains the non-septic infarcts found in acute and subacute bacterial endocarditis. The bland infarcts result from embolization of a fresh, less adherent and a more easily dislodged NBTE portion of the vegetation. One would hardly expect an embolus loaded with bacteria to become sterile after impaction in a stationary milieu of necrotic tissue where cellular and humoral mechanisms can act with difficulty, when the same immune factors are inadequate to sterilize the vegetation. Septic embolization occurs, but the high incidence of the bland infarcts encountered in septic and subacute bacterial endocarditis requires explanation.

APPLICATIONS TO BACTERIAL FORMS OF ENDOCARDITIS

It was recognized long ago that a bacterial endocarditis, usually of the subacute variety, could be encountered at autopsy in a "bacterial free stage." Vegetations in any one heart are occasionally encountered at autopsy showing foci of active bacterial proliferation with marked inflammatory changes in the regional tissue, bacterial-free vegetations with granulating and organizing fibrosis and calcification, as well as fresh NBTE without any underlying reaction, in a single case. More cases coming to autopsy now show the effects of therapy, and such transitions in both acute and subacute bacterial endocarditis are now frequent (28). The vegetations must be studied extensively by multiple sections to establish the variable pathological picture in a single case.

The underlying metabolic basis for NBTE determines not only the initial localization and format of bacterial vegetations but also the mechanism of local extension. Definitive bacterial vegetations extend by a progressive bacterial contamination of contiguous NBTE. This accounts for the character of broad extension in continuity of bacterial vegetations, seen so often, particularly in subacute endocarditis. In a subacute bacterial endocarditis complicating a rheumatic valve, it is the adjacent NBTE portion that often shows the characteristic "rheumatic histology" (24). The morphological transitional features between rheumatic verrucae and bacterial valvulitis (subacute) has been stressed by Clawson and Bell (29) and Von Glahn and Pappenheimer (30). Extending areas of bacterial vegetations do not result from inflammatory reaction or local bacterial spread. Such sites of extension often show histologically an absence of all inflammatory reaction, so characteristic of early NBTE, and an absence of bacteria in situ in that portion of the vegetation. This is unexpected if the local adjacent spread of the vegetation is due primarily to inflammatory extension of the infectious process.

Acute bacterial endocarditis is associated with acute toxic features and more severe illness and greater stress. In contrast, the subacute form presents a milder, more latent syndrome, while NBTE is asymptomatic. An active bacteremia usually initiates the acute valve lesion; a passive bacteremia is more often associated with the origin of the subacute vegetation. In the latter, the initiating bacteremia is apt to be fleeting; in acute endocarditis the bacteremia is often prolonged with an original picture of chills, temperature, and severe sepsis. Acute bacterial endocarditis differs from the subacute form by showing more virulent organisms and a more frequent tendency to involve a normal valve structure not altered by previous damage. This implies that the septic virulent organism that seeded the vegetation is associated with a stressful toxic state sufficient to alter the enzymatic control and vitality of the connective tissue of the normal valve, even without a previous "devitalization" of the valve substance inherent in a former scarring process.

NBTE can appear with relatively little stress on the scarred and aged valve. An asymptomatic incidental bacteremia, as of a tooth extraction, seeds the NBTE and subacute bacterial endocarditis follows. This is an explanation for the association of subacute bacterial endocarditis with the rheumatic or scarred valve in the young. However, the healthy valve requires the severe stress of an active bacteremia to cause the initial NBTE, which upon infection with the virulent organisms from the associated, more prolonged bacteremia, yields acute bacterial endocarditis. The association of acute bacterial endocarditis with the healthy valve can be understood on this basis. In the aged valve, both acute and subacute bacterial valvulitis occur. Instances of acute bacterial endocarditis, considered to be bacterial from the outset, represent vegetations infected early. Thus, the clinical picture before and following the development of the different forms of endocarditis seems to correlate well with what one would expect on theoretical grounds.

THE CLASSIFICATION OF ENDOCARDITIS

The classical forms of endocarditis are seen at autopsy at particular stages of their pathological evolution with a remarkable constancy because they are associated with clinical syndromes of corresponding morbidity and mortality, with the equivalent clinical picture, i.e., short severe or prolonged milder clinical course with lethal outcome, frequent healing or complete absence of symptoms. Transition between all the classical pathological forms of vegetations, in both the non-bacterial and the bacterial groups (Fig. 2) are noted in clinical experience, at autopsy and in experimental lesions.

This feature of transition and the lack of demarcation of the classical entities has been emphasized by Karsner (31), Von Glahn and Pappenheimer, (30) Keefer (32), Allen (33), Moore (6) and others. The transitions between the rheumatic lesions and subacute bacterial and its bacterial-free stage have caused controversy with differing explanations (29). The differentiation of acute bacterial endocarditis from the subacute also presents difficulties, because the proffered etiological bacteria do not initiate the process but appear secondarily. One can

understand why a *Streptococcus viridans* can give the acute pathologic picture occasionally and a hemolytic *Streptococcus* can be associated with the subacute form of valvulitis. The reason for the transitions encountered between the two, grossly and microscopically, becomes clear as well as the rare change from one organism to another.

There has been a compulsion to classify the lesions of endocarditis morphologically in specific categories and to correlate these entities with particular etiological agents. The difficulties encountered in classifying a particular lesion are not due to our own inadequacy or ineptitude. They are inherent in the pathogenic mechanism. Transitional and overlapping stages between the more common individual morphological expressions of these diseases, i.e., the classical entities, must be expected, because the multifarious specific agents and definitive causative factors act through a common background mechanism which has only a limited range of morphological expression. It would be arbitrary to insist on absolute separate and independent classical categories bearing no relationship to each other, when, in fact, a continuity of relationship is inevitable because the different etiological and pathological mechanisms act through a fundamentally common parallel and therefore unifying process.

SUMMARY

Vegetative endocarditis is presented as due to a metabolic alteration of the valvular connective tissue, with subsequent blood protein precipitation. The primary change is biochemical and is non-infectious. It is non-specific and can be produced by several different mechanisms.

Vegetations similar to thrombotic non-bacterial endocarditis were produced on the valves of rabbits by repeated injection of dead bacterial cultures, and in rats by repeated tumbling, by exposure to cold, to simulated high altitude, and to high and low oxygen tension.

The initial lesion is a localized "edematous" swelling, resembling the edema of the edge of the valve seen commonly at autopsy. It is the earliest anatomical change in the valve induced experimentally.

The nature of the metabolic alteration is not established. The endocrine system plays an important role. Allergy and hypersensitivity may act not only through local action but also via the endocrine system; still the production of the initial lesion may be quite independent of such sensitivity.

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Thrombotic non-bacterial endocarditis is asymptomatic and silent, unless complicated by bacterial contamination, embolization, fibrosis or calcification. An explanation is offered for the frequent incidental finding of fresh thrombotic non-bacterial endocarditis at autopsy as a "terminal" vegetation.

The secondary changes of absorption, fibrinoid, organization or calcification in a non-bacterial thrombotic vegetation is determined by the nature and amount of altered valve substance proper, as against the fibrin and other blood elements present in the primary vegetation. Lytic absorption and fibrosis occur frequently

When healing occurs, valvular distortions follow and include fibrotic thickening with incorporation of chordae yielding elongation (billowing-sail distortion) or shortening and fusion (valvular stenosis) and calcification in and on the valve. The secondary changes following recurrent incomplete absorption of the early "edema" lesion and of the thrombotic non-bacterial endocarditis constitute an important cause of gross valve distortion.

A better understanding of the role of thrombotic non-bacterial vegetations in the general pathology of embolization follows, including an appreciation of the sites of origin, incidence and the occurrence of bland infarcts in bacterial endocarditis.

* * * * *

The localization of all vegetations on normal and scarred heart valve structures, rather than at other sites, is better comprehended.

Bacterial vegetative endocarditis is considered to be the result of a seeding contamination of the surface of this initial metabolic lesion of the valve.

To produce lesions of bacterial vegetative endocarditis in rabbits, repeated intravenous inoculations with dead *Streptococcus fecalis* were followed by a single injection of live organisms. Without such initial preparatory metabolic alteration of their heart valves, a single intravenous injection of living micro-organisms does not yield bacterial endocarditis in rabbits.

Local extension of a bacterial vegetation is the result of infection of an adjacent thrombotic lesion that is originally non-bacterial, and not merely the consequence of an extending bacterial inflammatory reaction.

The changing age incidence for all forms of endocarditis, with increase in the aged group, becomes accountable.

* * * * *

Transitions between the separate classical thrombotic non-bacterial lesions are encountered at autopsy. Also bacterial endocarditis has shown transitional features mindful of non-bacterial thrombotic, healing thrombotic and rheumatic vegetations. Gradations between acute and subacute bacterial endocarditis are similarly explicable.

With effective but inadequate anti-microbial agents, autopsies now show more instances of partial healing in the bacterial forms of vegetative endocarditis, with additional transitional instances resulting.

Increasing knowledge of the role of the thrombotic non-bacterial vegetation is elucidating the clinical syndromes of the separate types of endocarditis and is offering a rational basis for their characteristic features.

A basis for the evolution of the distinctive classical morphological forms of endocarditis is obtained and the standard pathological classification is more readily understood through application of the concept presented.

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THE ECOLOGIC ROLE OF THE PATHOLOGIST IN EVALUATING POTENTIALLY TOXIC SUBSTANCES

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Various portions of the population are constantly exposed, directly or indirectly, to environmental hazards such as products used for therapeutic, diagnostic, and cosmetic purposes; to substances used in agriculture such as insecticides, pesticides, and growth regulators; to food additives and preservatives; or to waste materials dispersed upon the ground, into the atmosphere, or into the world's water. These constitute potential risks and some of them threaten survival. Appropriate study is desirable to detect pathologic effects and to devise proper methods of prevention and therapy.

The assumption of safety is never justified. There are instances in which apparently innocuous substances were later found to be responsible for disastrous effects. The occurrence of retrolental fibrous dysplasia and blindness after excessive oxygen inhalation in premature infants is an example of unexpected peril due to an ubiquitous substance (1) (2) (3) (4) (5) (6). This condition is now responsible for most of the admissions of preschool children to North American institutions for the blind (7). A serious toxic effect is not blunted because it was unexpected, nor is tragedy less painful because a danger was not anticipated. We can never be overcautious in demanding that substances proposed for human use be safe. Even the acceptance of comparative safety on a statistical basis is of little consolation to the individual who becomes the unfortunate statistic. Therefore inertia, the magnitude of the undertaking or the cost should not deter appropriate detailed investigations. Indeed in this wonderful era of accelerated discovery, man will continue to live in an uneasy world charged with anxiety until toxicity studies keep pace with the new revelations.

A sound program for the study of an inordinate number and variety of potentially toxic substances has not as yet been evolved. There are no existing slide rule plans for guidance. Since the experiments are conducted in animals, the results can never be directly extrapolated to man. Certainly, toxicity studies may be at times overwhelmingly dull and tedious, and therefore most often create disinterest. As a consequence some areas have been superficially studied and only those few which have enjoyed popular appeal, have been intensively investigated. Nevertheless, human contact with any aleatory substance, even when mass populations are not exposed, places a firm obligation upon the investigators to determine, before the substance is released for use, whether it will under any circumstances produce any ill effects. For example Dulcin, (p-phenethylurea) which is 200 times as sweet as sugar could not be used for human consumption because it produced liver tumors in animals (8). Remedies used in the amelioration of fatal maladies such as cancer, are often used with greater

From the Laboratories of the Joseph and Helen Yeamans Levy Foundation, Beth Israel Hospital, New York City.

latitude than remedies directed towards the treatment of specific diseases which of themselves are not fatal and often are self-limiting. Even in the former sector of therapy, benefits must outweigh detrimental effects, and iatrogenic results must not be serious. On the obverse, we cannot condemn, discard, or restrict from full use a drug which may be helpful to a segment of the population suffering from a serious or fatal malady because of side effects.

In a different vein, knowledge of the toxicological behavior of a substance may lead to the creation of new and non-toxic variants of the substance. This is well brought out in the work of Swick (9) who observed that selectan neutral with its methyl group was extremely toxic. This observation led him to a derivative in which the N-methyl group was replaced by a sodium glycinate moiety. The modified compound uroselectan, was more soluble and not toxic, and thus was the first drug to be used clinically for visualizing the kidney roentgenographically.

The pharmacologist and other scientists determine effects of drugs and use this knowledge in the treatment of disturbed functions. The pathologist plays a fundamental role in the study of potentially toxic effects as manifest by morphologic changes in the various organs. He is concerned not only with the effects of the drugs upon the disease process, but also with toxic effects of the drug upon the host. Investigations in the other scientific disciplines pursuing such researches are important factors in this joint endeavor, but they often lay stress on or limit themselves to more or less specific effects on particular tissues or organs. The pathologist, on the other hand, is uniquely equipped to consider the total picture, at least insofar as pathologic anatomy is concerned, since he administers the drug at increasing dose levels to intact living animals, both healthy control and abnormal. After observing the clinical reaction, the tissues are subjected to gross pathologic and detailed histologic study, thus targeting those organs subject to pathological changes. In some instances, the results may be wholly unexpected; for example, when sulfapyridine was administered to rats, kidney stones were found at autopsy (10). These findings were reported to the medical profession before the drug was released for human therapy. After the experimental findings were reported, the clinician was alerted to the potential complication (11), and was thus able to take all possible precautions to detect, prevent, or ameliorate untoward effects. Nevertheless, the question of the suitability of this drug for human use was properly raised and evaluated. At that time, sulfapyridine was the only drug available for use in the treatment of lobar pneumonia. Because that form of pneumonia was attended with a high mortality, particularly in the aged, it was decided that sulfapyridine, in spite of its toxicity, should be released for human use, with the warning to perform frequent urinalysis in order to detect hematuria and urolith formation. The dispatch with which the Food and Drug Administration arrived at this decision was commendable. That Federal body did not delay, but promptly approved the use of this drug which radically lowered the morbidity and mortality of lobar pneumonia and other infectious processes.

To study the toxic manifestations of a compound, a comprehensive plan is required. It will be necessary soundly to devise, appraise, improve and modify until a practical routine with a proper perspective is established. And even then,

of the great number of substances, many will require individualized study. In each instance the limits of safety must be known. Should any hazard exist, even with massive doses, preventive procedures and methods of counteracting toxic effects should be established. Even after the development of a study plan, the task of the morphologist will not be an easy one, since characterization of morphologic changes after the administration of a single substance to a normal animal is not simple. Specific primary changes produced by the substance must be differentiated from changes secondary to shock, inanition, supervening infection, or healing effects (12). In addition, the changes must be distinguished from morphologic alterations produced by temporary or permanent inhibition or stimulation of endocrine or other visceral functions, such as the hypoactivity of the pituitary, thyroid, and adrenal glands seen after the administration of large doses of cortisone (13), or conversely, the hyperactivity of these glands observed after administration of sulfapyridine (14). With substances that are produced physiologically, for example, cortisone or ACTH, it is necessary to differentiate the changes dependent upon physiological mechanisms from those produced as a result of pharmaco-therapeutic or toxic effects (15) (16). A normally produced physiologic substance, such as a hormone, when given in large doses, may cause a compensatory atrophy of the very cells which produce it (13) (17) (18). Under these conditions, there will be no deficiency of the substance administered; however, since these same cells elaborate other vital compounds, the depression or atrophy of these cells will produce deficiencies of all other substances normally elaborated by those cells (16) (17). Disturbances in adaptive balance mechanisms also require interpretation. In the pregnant animal there is a considerable alteration both structurally and functionally of vital organs. Toxic materials will act differently upon those organs than they would upon the organs of the non-pregnant animal. Thus, the mammary gland of the pregnant mouse shows an exaggerated enlargement after the administration of cortisone, an effect which does not occur in the non-pregnant mouse (19). Similarly, chlorophyllin in the normal mouse is merely taken up by the reticulo-endothelial system, but in the pregnant animal it produces thrombi in portal radicals, as well as a liver necrosis (20). When substances are administered to pregnant animals, direct effects on the fetus or nursling must be considered as well as indirect effects brought about by derangement of the endocrines of mother. In the mouse, following large doses of cortisone given 7 to 8 days before parturition, fetuses die *in utero*, showing signs of retarded development and often autolysis. If given later in the course of pregnancy, the young are born alive but die within 2-5 days (19). Fraser and Faunstat (21) produced congenital malformations with cortisone. In our own laboratories, Dr. Glaubach has shown that the administration of cortisone to mice 9-12 days after parturition retarded the growth of the nurslings and produced a sparseness of hair. Normally, the male grows faster than the female from the 20th day of age, but in these experiments, the male offspring did not show the expected rate of growth until 40 days of age (22).

In studying the effects of drugs, attention must be paid to the dose, the rate of absorption, the vehicle in which the compound is dissolved or suspended and

the routes of administration. All methods of exposure to the substance must be studied in order to draw competent conclusions of its relative safety or danger. Exposure should include absorption through the skin as well as by way of the respiratory passages and other routes. When anesthesia is used in an experiment, the influence of the anesthetic must be evaluated. The possibility of addiction must also be ruled out. In addition, the permanency or reversibility of morphologic changes must be considered. The age of the animal used in testing is important in evaluating the effects of a given substance; thus, riboflavin protects young rats against liver tumors (23) (24), but in older rats, riboflavin affords no protection (24). The nutritional status of the animal is of great importance as is the diet and the handling. It is well known that malnutrition, stress, or excitement cause changes which influence body fluids and tissues. In excited animals the altered peripheral blood picture resembles that produced by cortisone (25). The effects of the compound on the defense mechanisms, including antibodies, must also be considered. The importance of this has been amply shown with cortisone (13) (17) (26).

It is apparent that the administration of a compound to a series of normal animals of one species is not enough to adumbrate the toxicity picture. Small doses of a compound may produce a toxic effect in one species, while large amounts may not produce the same result in another species. Such a species variation is well exemplified with sulfapyridine. In the monkey, 0.25 gm. per kilogram is necessary to produce kidney stones; in the rat 5.0 gm. per kilogram is required; in the rabbit the dose is 10 to 15 gm. per kilogram, and in the mouse, a species which does not acetylate the drug, kidney stones cannot be produced following an oral dose no matter how great (10). In the selection of animals for study, it is important to use different sources of supply of the same species since it has been shown that animals, even of the same strain, coming from different sources, may differ in reaction despite the fact that the growth curve, condition of the fur and the physical response to stimuli are normal. For example, animals from one source may harbor dormant, "undetectable", infections which can be detected only after the administration of cortisone or exposure to a stress-producing stimulus such as x-ray or hemorrhage (17) (27) (28). It is immediately apparent that a given drug or substance may produce different effects in normal and diseased animals, but in animals carrying a dormant sub-clinical infection, the source of such differences is more subtle. C-57 mice received from one dealer succumbed to infection within 12-15 days after being exposed to 600 r total body radiation. The same strain of mice obtained from another source which did not harbor a subclinical infection died in about 9 months from kidney and vascular disease or tumors (29). In this way, it was possible to distinguish between immediate and delayed effects of x-ray (29) (30) (31). A well-planned experiment may be rendered valueless because of the activation of a dormant infection. It has also been shown that the immune animal may react differently from the non-immune animal. Similarly, an animal with a diminished kidney function may frequently show changes more dramatically after a small dose of a substance than a normal animal will after a larger dose. The same may be said

of animals with impaired liver function as well as those with an impaired thyroid function. It is of interest to note that the administration of chlorophyllin to C-57 mice bearing carcinoma 755 caused liver necrosis and venous thrombosis, which does not occur in the normal non tumor-bearing mouse (32). It is also important to study the effects of agents upon animals which are susceptible to the spontaneous appearance of tumors. With susceptible animals, such as the C-58 mouse in which spontaneous leukemia almost always occurs, it may be possible to hasten or retard the appearance of leukemia.

Much of the foregoing has been concerned with drugs and related products, but many other substances must be studied. These include growth and ripening regulators used on agricultural products, food additives and preservatives, pesticides, and water, soil and air borne wastes. Some of the problems of water borne waste products have received considerable attention, but certainly not all have been subjected to sufficient study. Pathological changes produced by waste products released into the atmosphere with possibly a single exception, that of radioactive products, have not been intensively studied and evaluated. The effects of all of these contaminants upon plant, insect, and animal life must be ascertained. Other toxicological studies must concern themselves with the effects of synthetic fabrics, dyes, shoes, insole accessories, and polish. It is important to note particularly in these instances and with pesticides and wetting agents that absorption through the skin may produce greater toxic results than absorption by other routes; for example, dieldrin and aldrin pesticides are 10 times more toxic by surface absorption than by oral ingestion (8).

The importance of air borne waste products recalls an experience of mine in the summer of 1930 when a large group of individuals living in a localized area of a city appeared in the emergency room at night with complaints of severe asthmatic attacks. On other nights, individuals from other localized areas appeared with the same complaint, but on a single night the individuals always came from a single, limited, almost delineated, zone of the city. This remained an enigma until it was ascertained that a castor bean processing plant in the city expelled its exhaust into the air. It was then recognized that the vagaries of the winds determined which areas would be deluged with the effluvia of the processing plant (33).

When mass populations are to be exposed for prolonged periods of time to a substance, it is self-evident that great assurances of safety must be on hand. These assurances can only come from studies which extend over the life span of the animal and of the progeny for generations since the effects are not always apparent and may be latent for long periods. In this way the influence of the substance upon fertility, the aging process and life expectancy can also be determined. In order to bring out pathological changes, increasing dose levels must be administered to different groups of animals. The highest dose which induces no pathology must be determined and at least one dose level should be sufficiently great to produce frank pathology or death. There are some who believe this extension to extremes to be unreasonable, but it is felt that in this manner even the remotest possibilities will be known, particularly since species reaction is so

variable. Once the effect of a high dose level is known, one may seek with great detail at lower dose levels for histochemical or pharmacological changes which may not be anatomically apparent. Further, the very process of inducing pathological changes in experimental animals frequently leads to new knowledge. The finding of urolithiasis after the administration of sulfapyridine led to fundamental divergent studies including angiotoxic, nephrotoxic, and other organ effects (34) (35) (36) (37); the changes in the spinal cords of animals receiving large doses of pyridoxine afforded a tool for the investigation of demyelinating processes in the central nervous system (38); the finding of renal changes with rapid development of visceral and vascular calcification after the administration of large doses of riboflavin (39) similar to those after sulfonamide derivatives (36) (37) can be used in the study of calcium metabolism (39); the congenital anomalies produced in the rat by feeding excessive amounts of Vitamin A makes possible the study of these unusual malformations (40) (41).

CONCLUSION

1. There is an urgent need for carefully controlled toxicological studies of an ever-increasing array of substances to which the population is exposed. These substances include products used for therapeutic and diagnostic purposes, for agriculture and animal husbandry, as chemical food additives, ripening agents and preservatives and the waste materials dispersed into the atmosphere, the ground or water.

2. No standard systematic plan for the toxicological evaluation of all these potentially dangerous substances has yet been evolved. In seeking a general plan for the evaluation of potentially toxic substances, it will be necessary to assess existing methods, to devise new approaches, and to improve and modify until a practical plan with a proper perspective is established. The pathologist can contribute greatly in these ecologic studies (42).

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TUMORS OF THE SOFT SOMATIC TISSUES

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The soft somatic tissues constitute the greatest amount of tissue within the human organism. This mass of flesh, situated between the epidermis and the parenchymal organs, comprises over 50 per cent of body weight. The muscles alone, of which there are over four hundred, constitute 40 to 45 per cent of body weight of the adult and about 25 per cent of the child's weight. A large number of specific tissue types comprise the soft somatic organs. These consist of connective tissue, blood, fat, lymphatic vessels, smooth and striated muscle, fascia, synovial structures, the reticulo-endothelium, and others. Offshoots of these tissues penetrate into every portion of the human anatomy. No organ is exempt from their presence.

The organs comprised by the soft somatic tissues are subject to injury and disease as are any other tissues. It is truly remarkable that until recently few efforts had been made to investigate the diseases to which the soft somatic tissues are subject. Infectious processes, hyperplastic phenomena, metabolic alterations, degenerative changes, and neoplastic growths may occur within the tissues that comprise the soft somatic organs (1).

The brilliant studies of Klemperer served to classify such apparently diverse pathologic entities as rheumatic fever, rheumatoid arthritis, polyarteritis, acute lupus erythematosus, scleroderma, and dermatomyositis under the common generic heading of Diseases of the Connective Tissue (2). These diseases are characterized by qualitative and quantitative changes of the connective tissue, especially the extracellular components (fibrous structures and amorphous ground substance). The pathognomonic alterations consist of fibrinoid collagen damage. "Fibrinoid changes" is a term applied to the collagen fibers which adopt the staining and structural qualities of fibrin that may represent an alteration of the fibers with either degeneration into or impregnation of fibrin. The exact nature is not known but the abnormal fibers that are fibrinoid may be the result of abnormalities in their chemical composition with the possible production of an abnormal protein moiety.

Klemperer's studies focused upon the extracellular compartment as an organ which could be diffusely diseased. This concept is important from the standpoint of neoplasia because chemical alterations of the fluid composition of growing fibroblasts result in malignant tumors (3). Stewart has demonstrated that fibroblasts in tissue culture become malignant when 20-methylcholanthrene is added to the culture media; and when these altered fibroblasts are injected into animals, sarcoma, demonstrating all the manifestations of malignancy, will develop at the site of the transplantation (4). Netteship studied the sequence of events

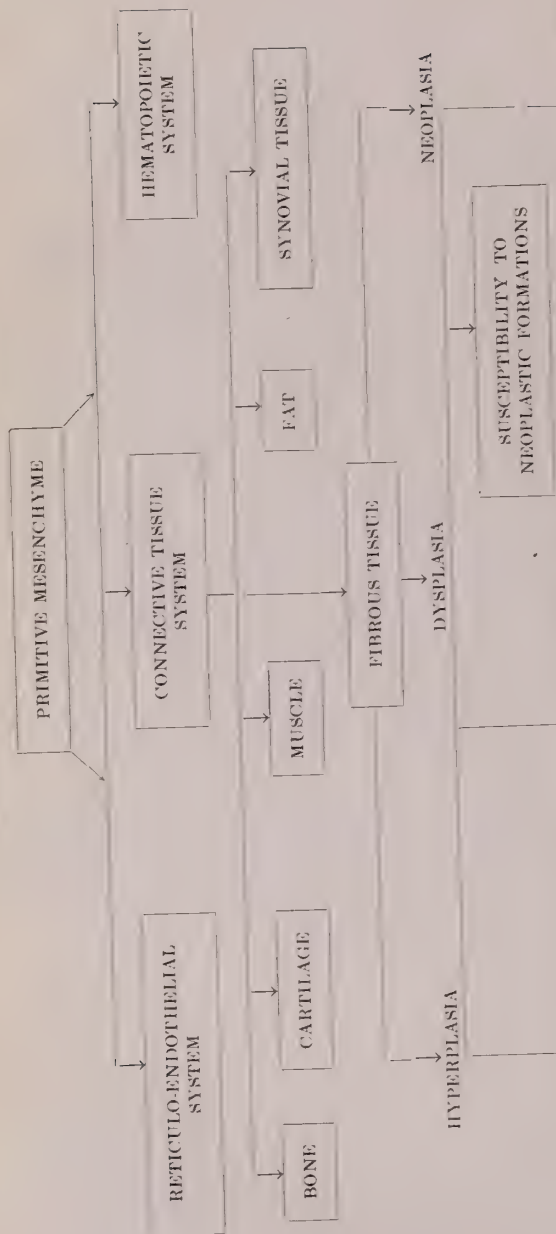
after the injection of 20-methylcholanthrene into hamsters. Within 24 hours after injection, marked edema of the connective tissue develops and certain connective tissue cells are found detached from the others and are swollen and granular. These cells, altered within 24 hours after injection of the cancerogen, develop into frank sarcoma in a smooth, gradual manner during a brief period. The altered cells proliferate and are present in groups, and then large sheets of them are noted and finally a sarcoma develops (5). These animal experiments suggest the possibility that alterations in the fluid medium which bathes these cellular components of the fibrous tissue network may possibly play a role in inducing sarcomas in humans. Table I presents our classification of pathologic involvements of fibrous tissue.

Neoplasms of the soft somatic tissues have, for some unknown reason, received scant attention regarding their nosology, natural history, and methods of treatment. This is truly remarkable in that this tissue, which comprises the bulk of the human body, is subject to a host of neoplastic afflictions that vary from very benign growths to some of the most malignant. Such tumors have frequently been described under the nondescript generic heading of sarcoma, and have been lumped into this nosologic repository without effort to identify and further subdivide, and thereby learn about and conquer the various subdivisions. Stimulated by the success of Klemperer in classifying and cataloguing many metabolic derangements of this system, attempts have been made to understand better each of the tumors arising from the soft somatic tissues.

At the combined symposium of the National Cancer Institute and the American Cancer Society held in 1949 (4), the panel on tumors of the soft somatic tissues represented a high light in efforts to understand better this oncologic entity. This meeting, at which Dr. Arthur Purdy Stout presided and in which some of the leading students of tumors of the soft somatic tissues participated, represented an effort to subdivide various tumors of this group so that definitive methods of treatment could be developed.

An outstanding contribution of this meeting was the presentation of a classification of tumors of the soft somatic tissues. This classification, slightly modified by us, is presented in Table II. It is of interest that it includes 56 tumors or tumorlike growths, exclusive of the lymphatic and reticulo-endothelial tissue; of these 34 are benign and 22 are malignant. Each of these growths represents an individual disease process with its own characteristic natural history, method of dissemination, and means of growth, and, accordingly, demands specific methods of treatment (5). The large clinical patterns of these various processes are evident. Some of the largest tumors of human oncology are included (the huge lipomas and cystosarcoma phylloides). Some of the most painful neoplasms occur here (the glomus tumor which, despite its extremely small size, is exquisitely tender and painful). Some of the growths (the dermatofibrosarcoma protuberans) remain locally limited, grow to huge proportions, and practically never metastasize (6) (Fig. 1). Others have metastasized and are present in large numbers at the time the diagnosis is made, even though the primary tumor may be very small (Kaposi's hemorrhagic sarcoma). Some grow to a limited size and remain quies-

TABLE I
The nosology of pathologic involvements of fibrous tissue



		Mixed Neoplasms	
		Benign	Malignant
Fibrous Tissue Response to Cancer.	1. Stroma of most neoplasms	1. Fibroma (a) Pedunculated (b) Infiltrative	1. Dermatofibrosarcoma protuberans (Hoffman)
	2. Exaggerated carcinoma (breast)	2. Desmoid tumors (Desmoma)	2. Regional fibrosarcoma
	(a) Scirrhus	3. Fibrous elements	(a) Soft somatic tissues
	(b) Linitis plastica (stomach)	(a) Juvenile pharyngeal angiofibroma	(b) Alimentary tract
	(c) Hodgkin's disease	(b) Fibromyoma	(c) Breast
	Myositis ossificans		(d) Perosteum
			(e) Brain
			(f) Genito urinary system: Kidney, tunica vaginalis, penis
			(g) Lung
			(h) Pleura
			(i) Mediastinum
			(j) Trachea
			(k) Nasopharynx and others
			2. Fibrosarcomatous elements almost always present with other neoplasms of mesodermal origin
			Ex: Synovium, rhub-

TABLE II
*Classification of soft-part somatic tumors**

Type of Tissue	Benign Tumors	Malignant Tumors
1. Fibrous tissue	a. Fibroma b. Keloid c. Dupuytren's contracture; palmar and plantar fibro- matosis d. Peyronie's disease of penis; chronic fibrosing cavernitis e. Desmoid tumor of abdominal wall (desmoma) f. Progressive fibrosing myo- sitis (Meyenburg's disease) g. Dermatofibrosarcoma protuberans	a. Fibrosarcoma b. Dermatofibrosarcoma pro- tuberans
2. Undifferentiated mesenchyme	a. Myxoma b. Mesenchymoma	a. Myxoma b. Mixed-cell sarcoma (mesen- chymoma)
3. Heterotopic bone and cartilage	a. Myositis ossificans	a. Osteogenic sarcoma b. Chondrosarcoma
4. Adipose tissue	a. Lipoma (solitary and mul- tiple) b. Congenital diffuse lipomatosis	a. Liposarcoma
5. Blood and lymph vessels	a. Hemangioma b. Systemic angiomatosis c. Rendu-Osler-Weber's disease d. Neuro-angiomatous syn- dromes e. Lymphangioma f. Cystic hygroma g. Glomus tumor h. Hemangiopericytoma	a. Angiosarcoma b. Lymphangiosarcoma c. Angio-endothelioma d. Kaposi's idiopathic sarcoma e. Granulation-cell sarcoma f. Hemangiopericytoma
6. Lymphatic and reticuloendothelial tissue	?	a. Malignant lymphocytoma b. Reticulum-cell sarcoma c. Brill-Symmers disease; giant follicular lymphoma d. Mycosis fungoides e. Plasmacytoma f. Hodgkin's disease
7. Synovial mesothelium	a. Giant-cell tumor of tendon sheath b. Synovial xanthoma c. Hypertrophic arborescent synovioma of joints	a. Malignant synovioma (syn- ovial sarcoma)
8. Smooth muscle	a. Leiomyoma b. Dermatoleiomyoma	a. Leiomyosarcoma
9. Striated muscle	a. Rhabdomyoma b. Granular-cell myoblastoma	a. Rhabdomyosarcoma

TABLE II—(Continued)

Type of Tissue	Benign Tumors	Malignant Tumors
10. Peripheral nerves	a. Neurofibroma b. Neurofibromatosis (von Recklinghausen's disease) c. Schwannoma (neurilemmoma or peripheral fibroblastoma) d. Ganglioneuroma e. Paraganglioma (benign) <ol style="list-style-type: none"> 1. Carotid-body tumor 2. Pheochromocytoma 3. Carcinoid tumor? 	a. Malignant schwannoma b. Neurosarcoma c. Neurocytoma d. Paraganglioma (malignant) <ol style="list-style-type: none"> 1. Carotid-body tumor 2. Pheochromocytoma 3. Carcinoid tumor?

* This classification was modified from the working table adopted by the Panel on Soft-Part Tumors, Dr. Arthur Purdy Stout, Moderator. *In* Proceedings of the First National Cancer Conference, American Cancer Society and The National Cancer Institute, U. S. Public Health Service, 1949.

cent for the remainder of the patient's life (dermofibroma), whereas others afflict all of the mesodermal and ectodermal structures of the body and produce some of the most grotesque deformities seen in human pathology (some of the disseminated expressions of von Recklinghausen's disease, diffuse neurofibromatoses). One could describe indefinitely the bizarre types or combinations of types of affliction which are expressions of the growth patterns of this group of tumors.

Despite the tremendous headway made in the diagnosis of these neoplasms histologically, there remains a large number of tumors that present only characteristics of sarcoma with no criteria whatever pertaining to the tissue of origin. Thus, of 717 sarcomas reported by us (7, 8), 261 (36 per cent) could not be diagnosed as to their tissue of origin by such expert pathologists as Ewing, Stewart, and Higgins. The situation is further compounded when one recalls the great growth potentialities of the primitive mesenchyme and the fact that the various structures derived from it (the reticulo-endothelial system, the hematopoietic system, and the connective-tissue system including bone, cartilage, muscle, fat, synovial tissue, and fibrous tissue) are closely related to the primitive mesenchyme. It is therefore not surprising that under different stimuli marked and protean manifestations of this growth capacity develop. Furthermore, because of the ontogenetic relationship of these systems, it is not surprising to find different components of these systems participating in a given disease process. They even differentiate into one or another of the organs under certain stimuli, as in extramedullary hematopoiesis, etc.

INCIDENCE OF TUMORS OF THE SOFT SOMATIC TISSUES

It is practically impossible to evaluate the exact incidence of tumors of the soft somatic tissues. The difficulty is twofold: (a) many of the harmless benign tumors such as small hemangiomas, synovial ganglions, fibromas, etc. are so

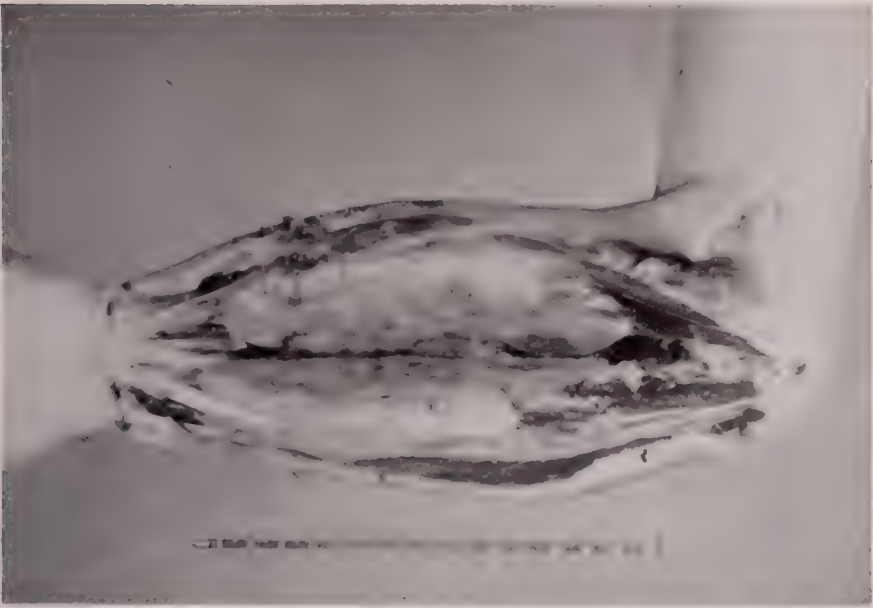


FIG. 1. A bulky dermatofibrosarcoma protuberans which was treated by wide excision and skin graft. Despite their huge size, these neoplasms have never been observed to metastasize. From Pack and Tabah (6).

innocuous as to be clinically insignificant; (b) many patients are either never referred for treatment or they are treated in the physician's office, with no attempt at statistical enumeration.

The actuarial statistical bureau of the Metropolitan Life Insurance Company reported that in 1950 there were 559 deaths in the United States from malignant neoplasms of connective tissue of unspecified sites, a death rate of 0.4 per 100,000. The total number of deaths from malignant neoplasms during that year was 210,733, with a death rate of 139.9 per 100,000.

On the Mixed Tumor Service of Memorial Center for Cancer and Allied Diseases and at the Pack Medical Group, a total of 717 patients bearing malignant tumors of the soft somatic tissues have been observed during a 25-year period (8). Sarcomas of the soft somatic tissues comprise 0.8 per cent of all malignant tumors. It is of interest that this value of 0.8 per cent of all malignant tumors coincides with the value obtained by the National Cancer Institute in a survey of all malignant tumors reported from ten urban areas of the United States.

INCIDENCE OF VARIOUS TYPES OF SARCOMAS

Table III presents the relative incidence of the different types of sarcomas. The greatest subdivision consists of sarcomas of undetermined histogenesis (36.4 per cent), which emphasizes the fact that many sarcomas observed to date are in a form which precludes their exact histogenic definition. The most frequent definable sarcomas were the liposarcomas (14.6 per cent) and the rhabdomyosarcomas (13.0 per cent). Synoviomias, Kaposi's sarcomas, and malignant

TABLE III

*Tumors of soft somatic tissues of infancy and childhood (incidence according to histologic type of tumor)**

Histologic type of tumor	Total No. cases	Patients 15 years of age and less	
		No.	Per cent
Total cases.....	717	51	7.1
Sarcoma of undetermined histogenesis.....	261	23	8.1
Liposarcoma.....	105	7	6.7
Rhabdomyosarcoma.....	100	4	4.0
Synovioma.....	60	3	5.0
Kaposi's sarcoma.....	48	0	0.0
Malignant neurilemmoma.....	46	7	15.2
Fibrosarcoma.....	39	4	10.3
Dermatofibrosarcoma protuberans.....	39	1	2.6
Angiosarcoma.....	19	2	10.5

* From Pack, G. T., and Ariel, I. M. (13).

neurilemmomas were more or less numerically equal. The relatively low incidence of fibrosarcomas in this group is significant in view of other statistics, in which fibrosarcomas dominate the histologic situation (9). For example, in the Presbyterian Hospital series of 432 primary sarcomas of soft parts, 184 were listed as fibrosarcomas (10). It is believed that many neoplasms catalogued as tumors of unknown histogenesis may be classified as fibrosarcomas in reports from other institutions. Angiosarcomas were the least frequently observed malignant tumors of soft somatic tissues in our series, comprising 2.6 per cent of the total.

DO SARCOMAS OF THE SOFT SOMATIC TISSUES METASTASIZE TO THE REGIONAL LYMPH NODES?

One of the fixed ideas that has wrongly persisted about the behavior of cancer is the opinion that sarcomas metastasize solely through the blood vascular system and carcinoma by way of the lymphatics. Although it is generally true that malignant tumors of mesenchymal derivation are blood-borne in their metastases, an appreciable number metastasize to the regional lymph nodes. This fact furnishes the indications and logic for the operation which we have employed and called "excision and dissection in continuity for primary tumors and metastases to regional lymph nodes."

Synovial sarcomas have metastasized to regional lymph nodes (Fig. 2) in 16.6 per cent of the patients studied (11). *Angiosarcomas* also metastasize to lymph nodes in a large percentage of cases; 45 per cent of the terminal cases of patients bearing angiosarcomas developed metastases to the regional lymph nodes. No patient with *Kaposi's hemorrhagic sarcoma* developed metastases to the lymph nodes in this series. That *rhabdomyosarcomas* do not develop distant metastases is surprising in view of the fact that the muscle contracts so frequently, offering a means of propulsion for any tumor emboli. Of 100 patients, metastases to lymph nodes were observed in six per cent at the time of therapy. It is noteworthy that



FIG. 2. Gross specimen of a synovial sarcoma of the wrist which had metastasized to the axilla, and for which an intrascapulothoracic amputation was performed. From Pack, Ehrlich, and Gentil, Surg., Gynec. & Obst., 84:1105, 1947.

in those patients who were not cured of their rhabdomyosarcomas, 15.4 per cent bore metastases to lymph nodes (12). *Fibrosarcomas* metastasized to lymph nodes in only three to five per cent of all instances observed (10) (Fig. 3).

SARCOMAS OF THE SOFT SOMATIC TISSUES IN INFANCY AND CHILDHOOD

Sarcomas of the soft somatic tissues of infants and children (13) represent a histologic and clinical entity which, although not common, nevertheless constitutes one of the major forms of cancer of the developing infant and child. The presence of a malignant neoplasm in a newborn infant offers material for great speculation concerning etiology and pathogenesis. The cancerogen must be potent, for it has a short period to exert its influence (a maximum of nine months). Table III shows the incidence of childhood sarcomas according to histologic types, and Table IV presents an analysis of the relationship of age to the incidence of certain malignant tumors.

Localized chemical aberrations within the embryo could be responsible for the formation of sarcomas of the soft somatic tissues. Sometimes maternal influences will produce localized effects—for example, rubella in the mother frequently produces cataracts in the human offspring. It has been shown in animals that



FIG. 3. Embryonal rhabdomyosarcoma in a 4-year-old child which had metastasized to the inguinal lymph nodes, producing marked swelling of the extremity. The horizontal line indicates the upper limit of the palpable metastatic deposit.

insulin given to the parent results in congenital deformities, possibly by altering intrauterine environment.

Selective Senility. The reason for the differences in the behavior of cancer in the very young from that in older individuals is not understood. Certain cancers can well be explained on the basis of Cohnheim's theory of misplaced cell rests. Another important factor is the difference between the anatomic and physiologic ages of different structures within the organism during a given age of the individual. Thus, at the time of birth certain organs, such as the thymus, may be considered aged and commencing toward their involutional state. Other structures (vaginal epithelium) may be mature as the result of maternal hormones; and others may lie dormant awaiting their selective stimuli to mature—for example, the breast. Owing to certain inborn errors of metabolism, a speeding up of the aging process occurs for either certain structures, such as the epidermis in xeroderma pigmentosa, or for the entire organism, as seen in the Ehlers-Danlos syndrome. An example of senility at birth is seen in the placenta. Its calcareous, fibrotic, atrophic, and vascular changes are characteristic of old age. The placenta

TABLE IV

*Malignant tumors which seem to have significant relationship with age periods**

		Age	Most frequent tumors
Infancy	1-10 months "At first the infant, mewling and puking in the nurse's arms"	Birth to independent nutrition	Wilms's adenomyosarcoma of the kidney, ocular glioma
Childhood	10 months to 7th or 8th year	To development of senses	Ocular glioma, Wilms' tumor
Presexual	8th to 14th year "And then the whining schoolboy, with his satchel and shiny morning face, creeping like snail unwillingly to school"	Intermediate stage between childhood and adulthood	Usually free of malignant tumors
Pubertal	To 28th year (males). To 24th year (females) "And then the lover sighing like furnace, with a woeful ballad made to his Mistress' eyebrow"	From puberty to end of growth period	Endothelial, myelomas, thymomas, gliosarcomas, testicular sarcoma
Maturity	"Then a soldier full of strange oaths, and bearded like the bard; And then the justice, in fair round belly with good capon lined"	From end of growth to sexual decline (males), menopause (females)	Great host of malignant tumors
Senescence	"Second childishness, and mere oblivion, sans teeth, sans eyes, sans taste, sans everything"	From menopause (females) and from sexual decline (males) to demise	Basal cell epithelioma of skin, squamous cell carcinoma of skin, lip, buccal mucosa, floor of mouth and vulva, carcinoma of prostate gland

* From Pack, G. T. and Ariel, I. M. (13).

has the shortest life of any human organ, yet at times it is subject to the development of cancer (chorioepithelioma). This cancer formation is in keeping with its anatomic age.

The more frequent occurrence of sarcomas in infants and children than in adults is not completely understood. Chronic irritation has been demonstrated to produce certain sarcomas, as sarcoma in a burn scar. Whether irritating factors excite neoplastic formation during prenatal life is not known.

As the individual becomes older and as a result of the normal metabolic wear

and tear of an organism, compounded by small stimuli for fibrous propagation from infection, trauma, or other noxious stimuli, it would seem that a richer soil for sarcomatous formation exists in the adult than in the child, but this situation does not prevail, as sarcomas occur more frequently in children than do neoplasms of epithelial structures.

It is beyond the scope of this discussion to pursue this fascinating line of thought further, but evidence is presented to indicate that prenatal influences can affect a localized segment of tissue with resultant formation of a sarcoma entirely localized. Contrary to certain opinions, it does not reflect a generalized abnormality of the supporting structures of the organism and is thus akin to most sarcomas in the adult.

The stimulus for certain neoplasms is transmitted from parent to offspring by way of the genes and adheres to genetic laws—for example, retinoblastoma, hereditary cartilaginous exostosis, familial polyposis of the colon, and multiple neurofibromatosis and lipomatosis as well.

PRINCIPLES OF TREATMENT OF CHILDHOOD SARCOMAS

In most sarcomas of the soft somatic tissues, either a limited portion of tissue has undergone sarcomatous transformation, as in rhabdomyosarcoma, or a larger segment of tissue may be doomed to sarcomatous formation which occurs at variable postnatal periods. For example, neurilemmoma may invade an entire major nerve trunk from its point of emergence from the spinal tract to its fibrillar ramifications.

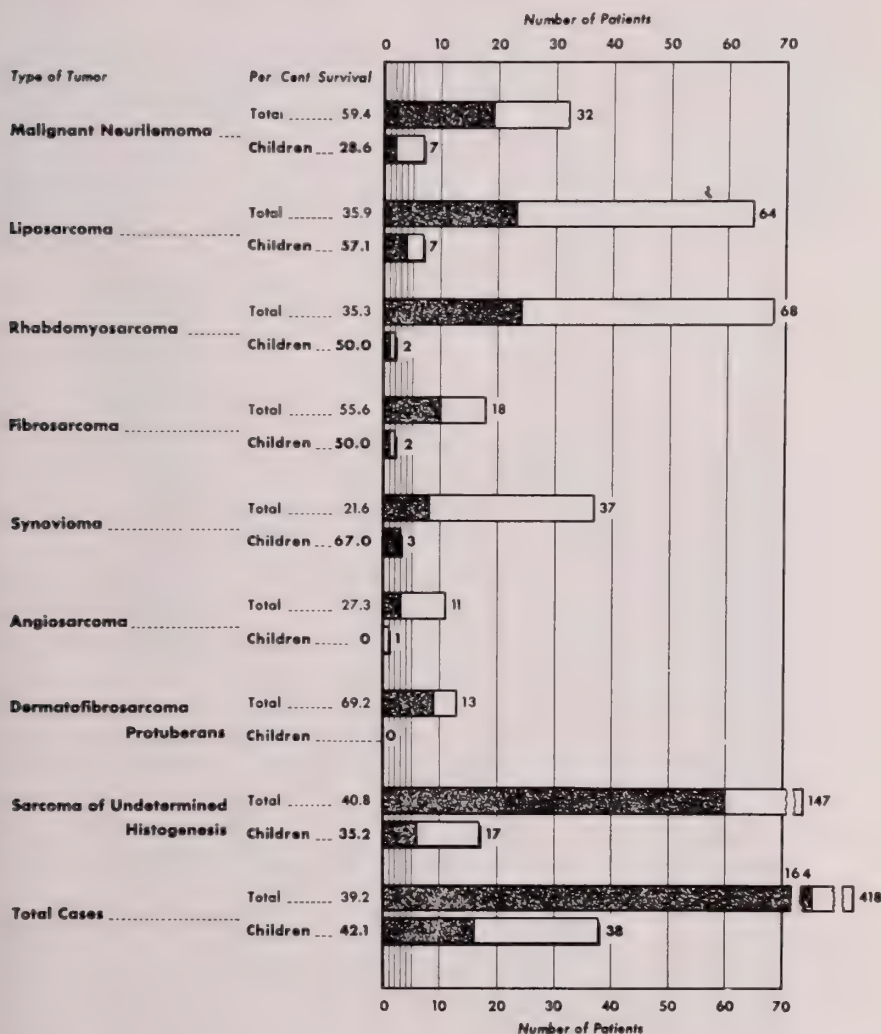
Such ontogenetic background aids in formulating principles for treating sarcomas of the soft somatic tissues in the infant and child. It forces the physician to seek out the presence of certain neoplasms if a parent had suffered its presence (example, retinoblastoma); it offers the surgeon criteria for extirpating organs which are the seat of certain premalignant tumefactions (familial colonic polyps); and it routes the surgeon on his course for boldly treating localized sarcomas of the soft tissues in infants and children. The knowledge that they represent localized and at times limited tissue aberrations and not generalized structural dysfunction permits the surgeon to strive for complete eradication of the neoplasm and its bed.

Infants and children tolerate radical operative procedures remarkably well; hence, none should be deprived of the benefits of a curative surgical attempt. So-called inoperability because of "frailty of the infant" usually reflects a frailty of the surgeon.

Analysis of the 51 sarcomas of the soft somatic tissues in infants and children in our series, moreover, reveals that not infrequently a histologically malignant neoplasm will manifest a rather benign clinical course and be subject to cure, whereas in the adult the outcome would more frequently be fatal. Table V presents the survival rates of the different histologic subdivisions of this series. Certain tumors in infants and children considered radioresistant on histologic criteria will respond dramatically to irradiation. Certain sarcomas in children

TABLE V

MALIGNANT TUMORS OF SOFT SOMATIC TISSUES

COMPARISON OF SURVIVAL
IN INFANCY AND CHILDHOOD WITH TOTAL SURVIVALS

have been described as reverting to a benign status either spontaneously or following irradiation; for example, neuroblastoma which reverts to a ganglioneuroma (14).

The observation that most sarcomas of the soft somatic tissues in children represent a localized growth originating, usually, in a single nidus, combined with the fact that 42.1 per cent of all children bearing sarcomas of the soft somatic

tissues treated by the authors have survived five years and longer, are hopeful signs.

THE TREATMENT OF TUMORS OF THE SOFT SOMATIC TISSUES

Reliance is placed upon surgical extirpation. The extent and type of operation depend upon the histologic type of tumor, knowledge of the natural history of this type of sarcoma, the location of the neoplasm, its size and extent, as well as the amount of tissue comprised by the neoplasm. Whether the neoplasm is primary or recurrent will influence treatment.

All benign tumors of the soft tissues should be locally excised. Although few of these become malignant, we have seen this phenomenon occur with sufficient



FIG. 4. Clinical photograph demonstrating a huge liposarcoma in the popliteal region which had developed after numerous recurrences of benign lipomas in this region. The excision necessitated resection of the popliteal artery with restoration accomplished by end-to-end anastomosis of the severed artery.



FIG. 5. Gross specimen of a rhabdomyosarcoma, demonstrating involvement of the entire muscle by the tumor. From Pack and Eberhart (12).

frequency to advocate excision as a prophylactic measure in the presence of an asymptomatic benign mass (e. g., a lipoma of the mediastinum), providing the operation is not too mutilating or too hazardous. Certain lipomas, especially those which are extremely large, may undergo sarcomatous degeneration (Fig. 4). Although certain synovial sarcomas may develop from benign solid synovial tumors, we have never observed a synovial sarcoma to arise from a giant-cell tumor or xanthoma of a tendon sheath. Although benign hemangiomas and lymphangiomas practically never undergo malignant degeneration, an occasional case has been observed in which malignant transformation apparently had occurred many years after the administration of irradiation for the original benign hemangioma or lymphangioma. In approximately 10 per cent of patients with diffuse neurofibromatoses (von Recklinghausen's disease) a malignant transformation of the benign neoplasm will occur. Desmomas of the abdominal wall, usually labeled benign, have been observed to produce visceral metastases in a few instances. These data do indicate that the possibility of malignant transformation should be considered in evaluating a therapeutic program for a patient bearing a benign tumor of soft somatic tissues.

The natural history of the different sarcomas permits indices for planning the surgical attack. Thus, the tendency for rhabdomyosarcomas to arise from multicentric foci within a given muscle or muscle group dictates that the entire muscle or muscle group from origin to insertion should be extirpated for rhabdomyosarcoma (Fig. 5). The frequency with which an entire nerve plexus may be doomed to sarcomatous degeneration demands an extirpation of that entire nerve plexus to effect a cure. We have seen neurilemmomas resected from the forearm only to have another one form in a more proximal segment of the nerve, finally demanding a resection of all the nerve elements as they emerge from the vertebral foramina, which procedure of course necessitates a forequarter or intrascapulothoracic amputation.

The frequency with which synovial sarcoma metastasizes to lymph nodes

TABLE VI

Malignant tumors of the soft somatic tissues. Comparison of 5-year cure rate of all histologic types

Histologic type of tumor	Total No. cases	Determinate cases*	5-year cures	
			Number	Per cent
Total cases.....	717	418	164	39.2
Sarcoma of undetermined histogenesis	261	150	62	41.3
Rhabdomyosarcoma	105	65	22	33.8
Liposarcoma.....	100	64	23	35.9
Synovial sarcoma.....	60	37	8	21.6
Kaposi's sarcoma.....	48	28	8	28.6
Malignant neurilemmoma.....	46	32	19	59.4
Fibrosarcoma.....	39	18	10	55.6
Dermatofibrosarcoma protuberans.....	39	13	9	69.2
Angiosarcoma.....	19	11	3	27.3

* Treated more than 5 years previously; available for end result analysis.

From Pack, G. T. (8).

necessitates an excision of the regional lymph nodes en bloc with the primary sarcoma.

The high incidence of metastases from angiosarcomas to the lungs necessitates a careful preliminary survey, utilizing tomograms, to rule out the presence of metastases before subjecting the patient to a mutilating surgical procedure aimed at cure. Gentleness in tissue handling, which should be maintained in the surgical treatment of any sarcoma, must be delicately practiced in treating angiosarcoma because of the constant possibility of blood-borne dissemination that might be induced during the surgical séance.

The high recurrence rates of fibrosarcoma and dermatofibrosarcoma protuberans is evidence that the surgeon was unaware of the occult pseudopodial-like extensions of these tumors and the excision was accordingly too limited.

The great radiosensitivity of embryonal liposarcomas would make irradiation the therapeutic modality of choice for these neoplasms.

The sarcoma should be excised without it ever being seen by the surgeon. The pseudocapsule about the sarcoma, which is formed by compressed adjacent tissues, tempts the surgeon to perform an enucleation of the tumor. This should never be accomplished because there are invariably tumorous projections beyond this apparent capsule.

Consent for amputation should always be obtained before operations for sarcomas because oftentimes the degree of resection depends upon the local anatomic situation.

Because of the grave prognosis, the result of uncontrolled sarcomas, the surgeon must boldly and ruthlessly remove any tissue which compromises the total excision of the sarcoma, be it blood vessel, major muscle groups, nerves, or the entire extremity. Massive retroperitoneal sarcomas may necessitate the removal of visceral organs or parts of organs.

RESULTS OF TREATMENT

The end results of treatment of sarcomas, as reported by Pack, show an over-all cure rate of 39.2 per cent of all sarcomas in this series (8). The survival rates for the different histologic subdivisions are presented in Table VI.

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ISOLATED BONE LESIONS ASSOCIATED WITH ELLIPTICAL ERYTHROCYTES

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In several types of severe anemias, such as sickle cell anemia and thalassemia major, the excessive marrow activity is associated with skeletal abnormalities demonstrable by radiography (1, 2). These lesions include generalized increase of bone trabeculae, osteosclerosis and irregular areas of bone condensation and rarefaction. Bone lesions are usually absent in mild anemias. In the family which we studied three members each presented a solitary bone lesion associated with abnormal appearing erythrocytes and a mild anemia.

CASE REPORTS

The family consists of a mother, father and 7 children all of Italian extraction. All were subjected to physical examination, hematologic studies and complete skeletal X-rays, the results being summarized in Table I. The histories of the 3 members presenting bone lesions follow.

Case M

This 55 year old mother of seven children was found to be anemic in 1949 when she sought treatment for her moderate obesity. Hemoglobin was 11.0 gms. per cent at the time the anemia was discovered and subsequently ranged between 12.0 and 13.0 gms. per cent from 1949 to 1953. Her only symptom was recurrent pain in the right shoulder with associated paresthesias of the right hand. Physical examination, serology, and urinalysis have been normal throughout this period. Skeletal x-rays taken in 1954 as part of this study showed an irregular area of bone sclerosis in the distal metaphysis of the left femur (Fig. 1). No other bony abnormality was noted.

Case 7

This 15 year old school girl, daughter of Case M, was examined in October, 1953 because of recurrent episodes of pain in the region of the left iliac crest which had bothered her at roughly monthly intervals for the preceding two years. There was no tenderness at the site of pain and no history of trauma or relation of the pain to motion. Physical examination was unremarkable and x-rays of the painful area showed no disease, but in the metaphysis of the left femur there was a 1.5 centimeter cystic lesion (Fig. 2). Hemoglobin was 11 gms. per cent; RBC, 3.67 million per cu. mm.; WBC, 8,900 (polys, 62 per cent; lymphs, 36 per cent; monos, 2 per cent), serum bilirubin, 0.72 mg per 100 cc.; Van der Bergh reaction and RBC fragility were normal. Bone marrow differ-

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TABLE I

Case	Sex	Age	Hb. (Gm)	RBC (M)	Retic (%)	Total Bilirubin(mg 100 ml.)	Elongate Elliptical Cells %	Total Elliptical Cells	Aniso and Poi- kilo- cyto- sis	Micro- cytes	Target Cells	Physical Findings	X-ray Findings	Hemo- globin F
F	M	59	12.7	3.90	1.1	0.40	1.0	11.5	0	0	0	None	None	XX
M	F	54	11.0	4.00	2.0	0.52	31.5	75.5	+	+	0	None	*	XX
1	F	39	13.1	4.02	1.1	0.40	20.5	63.5	+	0	0	None	None	XX
2	F	36	11.0	3.47	1.1	0.50	26.0	76.5	0	0	0	None	None	None
3	M	33	12.7	4.38	1.5	0.70	7.0	38.5	+	+	+	None	None	XX
4	F	32	12.2	3.90	1.0	0.50	0	26.0	0	0	0	None	None	None
5	F	23	11.8	4.46	2.6	0.40	71.5	97.5	+	+	0	None	*	None
6	F	18	11.8	4.42	1.5	0.79	32.5	73.0	+	0	0	None	None	XX
7	F	16	11.0	3.67	2.4	0.72	24.0	66.5	+	+	+	None	*	XX

XX: Not tested.

* See case report

+ (4)

	Round	Roundish	Elliptical	Elongate Elliptical
Average Normal.....	51.7	38.1	10.0	0.2
Familial Elliptocytosis...	1.0-7.5	17.5-33.5	37.0-39.5	22.0-42.0

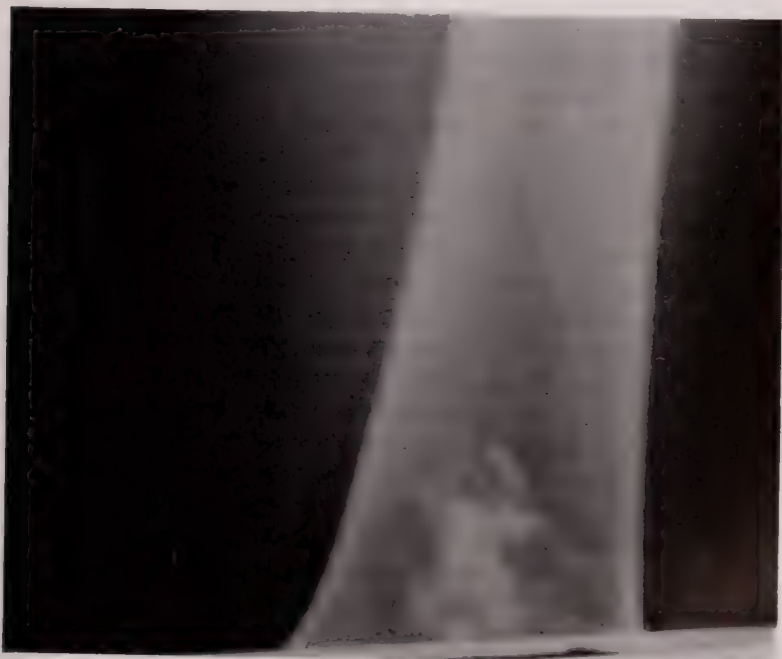


FIG. 1. Bone sclerosis in distal metaphysis of left femur, 55 year old woman (Case M).



FIG. 2. Cystic lesion in metaphysis of left femur, 15 year old girl (Case 7).

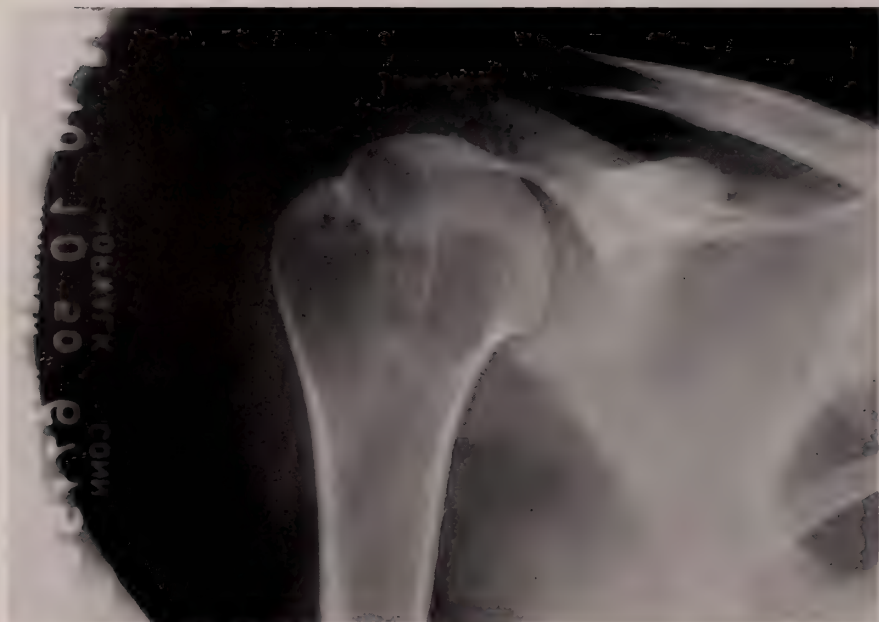


FIG. 3. Cystic lesion in head and neck of right humerus, 23 year old woman (Case 5).

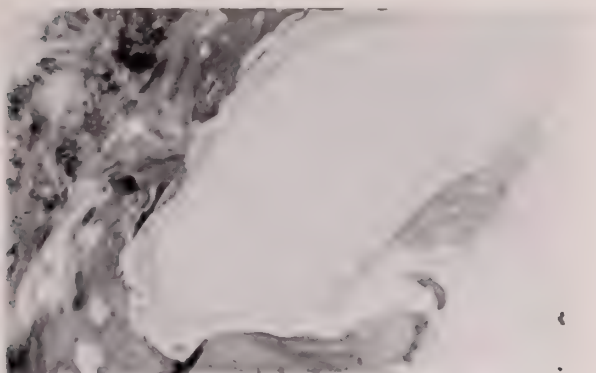


FIG. 4. Section of cystic lesion of bone, Case 5, magnification $\times 30$.

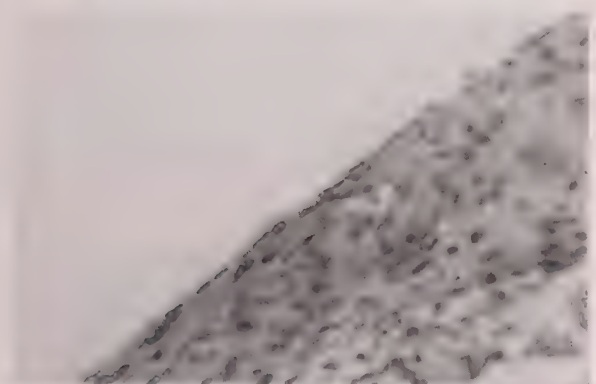


FIG. 5. Section of cyst wall made up of fibroblasts, Case 5, magnification $\times 400$.

ential was as follows: Histiocytes, 1.0 per cent; myeloblasts, 0.5 per cent; neutrophilic premyelocytes, 2.5 per cent; neutrophilic myelocytes, 6.5 per cent; eosinophilic myelocytes, 1.0 per cent; metamyelocytes, 5.5 per cent; stabs, 33.5 per cent; neutrophils, 17.0 per cent; eosinophils, 2.0 per cent; basophils, 0.5 per cent; lymphocytes, 14.5 per cent; monocytes, 0.5 per cent; plasma cells, 0.5 per cent; normoblasts A, 1.0 per cent; normoblasts B, 11.5 per cent; normoblasts C, 2.0 per cent.

On further observation, the pain gradually diminished but there was recent severe exacerbation in November 1954. Hemoglobin has remained at about 12.0 gms. per cent with continuous oral iron therapy.

Case 5

This 23 year old daughter of Case M was first seen in 1950 because of severe pain in the right shoulder. She had noted "clicking" of that joint for the preceding six years. Physical examination, serology and urinalysis were normal. A large cystic lesion in the head and neck of the right humerus was visualized by x-rays (Fig. 3) and confirmed surgically in 1950 when the cyst was unroofed, evacuated and filled with bone chips. Anemia, with the hemoglobin concentra-

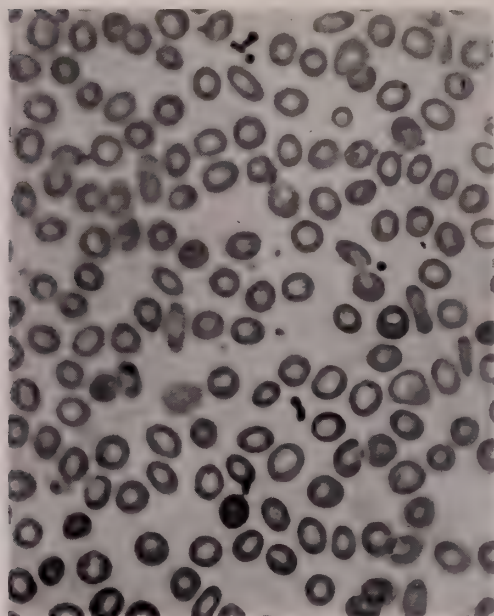


FIG. 6. Blood smear, Case M.

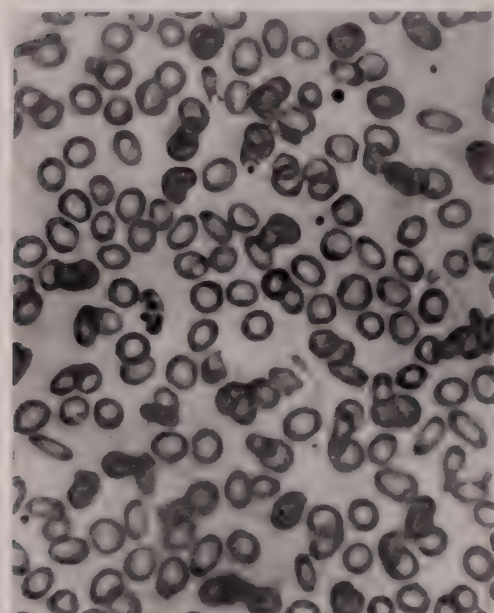


FIG. 7. Blood smear, Case 7.

tion of 10.0 gms. per cent was found on the initial examination and this has persisted with levels never in excess of 12.0 gms. per cent despite treatment with iron, folic acid, B12 and liver injections. There has been very little pain since surgery and on follow-up x-rays the lesion appears healed. Histopathologic ex-

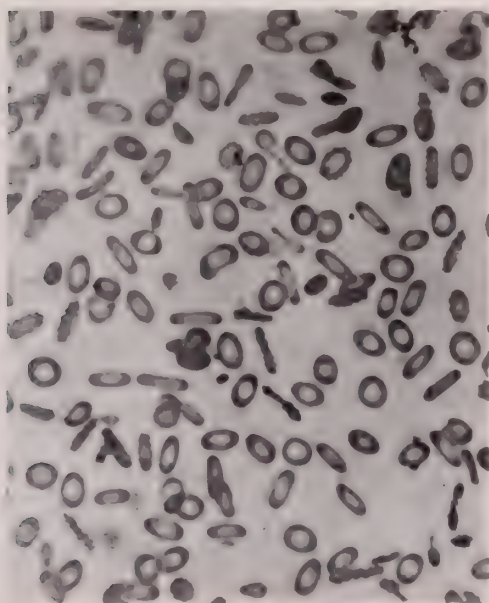


FIG. 8. Blood smear, Case 5.

amination of the numerous fragments of bone submitted was performed after decalcification. There were cavities filled with fibrous tissue in which were numerous juicy fibroblast nuclei (Figs. 4 and 5). Occasionally there were groups of osteoblasts and even some osteoid tissue. Osteoclastic activity was slight. Around the cysts were areas of sclerotic rather acellular bone. There were also some portions of normal bone containing hyperplastic bone marrow. The appearance was compatible with that of an old infarct or any nonspecific cyst. The presence of masses of tightly packed oval erythrocytes favored the idea of infarction but no thrombosed vessels could be found to substantiate such a theory.

DISCUSSION

The classification of the red cell abnormality in this family merits some discussion. The Italian ancestry and the presence of a case of frank Cooley's anemia in a nephew of the mother (case M) suggest that thalassemia minor might account for the red cell abnormalities particularly because Neel (3) feels that certain instances of thalassemia minor do present in this fashion, (that is, primarily as elliptocytosis). Furthermore target cells, anisocytosis, poikilocytosis and microcytes all are present in some members of the family. Against this presumption are the lack of compensatory polycythemia in any members of the family and the lack of hemoglobin F (by the alkaline denaturation technique) in the patients whose blood was studied for this substance. We therefore use the term elliptical erythrocytes in the title of this article in a purely descriptive sense, as we are unable to decide whether this abnormality represents true familial elliptocytosis, thalassemia minor, or a combination of both. Whether the bone lesions are associated hereditary abnormalities or are due to the blood dyscrasia cannot be ascertained at this time.

SUMMARY AND CONCLUSIONS

Isolated bone lesions which in two instances were symptomatic were found in a mother and two daughters. The family also presented slight anemia and peculiar erythrocytes, including many elliptical forms.

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THE RELATION OF VITAMIN A INTAKE TO CEREBROSPINAL FLUID PRESSURE: A REVIEW

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In this brief review I wish to call attention to the peculiar relationship between the intake of vitamin A and the cerebrospinal fluid pressure. Clinically this relationship is of particular interest to pediatricians as the condition of the fontanelle in the infant is so simple a guide in estimating intracranial fluid pressure, whereas in older individuals this pathological condition may be entirely overlooked. What makes a study of this relationship very fascinating is that increased pressure of the cerebrospinal fluid may appear both as a result of the intake of excessive amounts of vitamin A and also as a symptom of vitamin A deficiency.

INCREASED CEREBROSPINAL FLUID PRESSURE IN VITAMIN A DEFICIENCY

Vitamin A deficiency is not a commonly encountered condition in this country where the average diet includes milk which contains enough of the vitamin, rendering supplementation unnecessary. However, with the increasing frequency of the diagnosis "milk allergy," many infants are kept on vitamin A free diets, and if vitamin addition is neglected, the symptoms of avitaminosis A may appear. These symptoms result in a bizarre clinical syndrome including the following signs:

Retardation of mental and physical growth.

Anemia with or without splenomegaly.

Tendency to infection (skin and respiratory tract).

Epithelial metaplasia

In the eye: xerophthalmia and keratomalacia.

In the urinary tract: hematuria.

In the vagina: cornified epithelium.

In the digestive and respiratory tracts.

Endocrine disturbance: gynecomastia.

Increased cerebrospinal pressure with markedly bulging fontanelle.

Cranial nerve injury: facial paralysis.

As long ago as 1933 Blackfan and Wolbach (1) in a clinical and pathologic study of vitamin A deficiency described a 6 $\frac{1}{2}$ month infant, allergic to cow's milk, on a diet containing no vitamin A, who showed marked apathy and keratomalacia. "The neck was retracted and the sutures of the skull showed some separation." With vitamin A therapy, the infant recovered but remained blind. This is the first description of a human infant showing evidence of increased cerebrospinal fluid pressure due to vitamin A deficiency.

Cornfeld and Cooke (2) in 1952 and Bass and Caplan (3) in 1955 published cases of vitamin A deficiency including symptoms of markedly increased cere-

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brospinal fluid pressure. The following is a brief summary of Bass and Caplan's case:

A previously healthy infant at the age of a month developed severe generalized eczema for which he was put on a soy bean preparation, receiving in addition vitamin D (Drisdol) and vitamin C. He developed slowly so that at five months he weighed only $11\frac{3}{4}$ pounds. At seven months in the course of a mild upper respiratory infection with slight fever, he developed hematuria, for which he was hospitalized. Examination revealed severe anemia (hemoglobin 6.7 gms.), numerous minute corneal ulcerations, lethargy and complete anorexia. On the eleventh day extreme bulging of the fontanelle was noted with nuchal rigidity and rise in temperature to 104.2 degrees. Lumbar tap revealed normal fluid which rapidly reaccumulated. Skull X-ray, subdural and intraventricular taps proved negative.

The combination of anemia, corneal ulcers, hematuria and acute hydrocephalus led to the diagnosis of vitamin A deficiency. It was learned that the child had had no other food but Mull Soy, banana, peaches and rice. Vitamin A in large doses was given by intramuscular injection with dramatic results. The symptoms rapidly disappeared and the child made an uneventful recovery and has remained well.

The publication of this case led to the discovery a few months later of a similar one in New Jersey in a colored infant, also on a soy bean milk without added vitamin A. Beside malnutrition and xerophthalmia there was present a markedly bulging fontanelle with radiographic evidence of wide separation of the cranial sutures such as one sees in hydrocephalus. The blood level of vitamin A was zero. As in the above mentioned case, the administration of vitamin A resulted in rapid recovery.

Bass and Caplan (4) also described the sudden appearance of a markedly bulging fontanelle in a deeply icteric infant with avitaminosis A due to proven congenital absence of the bile ducts. When vitamin A was given by intramuscular injection, the distention of the fontanelle disappeared.

It has long been known that in experimental animals a diet deficient in vitamin A may give rise to definite changes in the nervous system including increased cerebrospinal pressure and hydrocephalus. These changes were blamed on faulty bone formation with resultant pressure on nerve trunks or on the brain itself. Thus Wolbach and Bessie (5) reporting on experiments on young mammals in 1941 say "The nervous lesions of vitamin A deficiency are wholly of mechanical origin, the genesis of which is a disproportionate growth of the central nervous system in relation to the bone which surround it." Again in 1955 Wolbach & Hagsted (6) investigating the same subject in young chicks conclude that "The neurologic disturbances of vitamin A deficiency in the chick are the result wholly of compression of the central nervous system produced by retardation of growth of vertebrae and bones of the cranium."

Sir Edward Mellanby (7) whose researches on this subject began as long ago as 1926, reviewed his findings in 1950. He was not quite as dogmatic about the neurologic disturbances, concluding that most of the degeneration could be ascribed to the fact that "a function of the vitamin A moiety was to control the activity of osteoblasts and osteoclasts, so that in its absence from the body, the bones were thickened and altered in shape, and that the incoordination was in fact, due largely, if not entirely, to the pressure on the nervous system of this thickened bone."

However, some investigators dealing with animals, long ago suspected that defects in bone growth might not be the sole cause of neurological disturbance. Moore (8) and his collaborators working with calves, wrote in 1935 "It seems doubtful that vitamin A could be concerned with such bone malformations as in the cases reported in this paper, but such an explanation might be plausible if the absence of vitamin A in some indirect way, raised the intracranial pressure." Again in 1939 he states "Vitamin A may possibly function to regulate intracranial pressure," and in 1940 (10) he concludes from further studies "A deficiency of vitamin A in the ration of the young bovine produces an increased cerebrospinal fluid pressure."

Recently considerable light has been thrown on this subject by the carefully controlled work of Millen (11) and his collaborators in England. Their papers deal directly with hydrocephalus due to experimental hypovitaminosis A. They have produced hydrocephalus in a very large percentage of the offspring of female rabbits kept for a long period on vitamin A free diet. The longer the animal was kept on this diet, the greater was the number of offspring with hydrocephalus. Their work shows that in the rabbit the increased intracranial pressure is definitely not dependent on abnormal bone formation. They say "The hypothesis that the primary factor in the pathogenesis of the condition is an overproduction of cerebrospinal fluid (Millen and others, 1954) receives additional corroboration from the result of the present experiments." They quote experiments by others in which increased pressure in vitamin A deficient animals rapidly falls after the restoration of the vitamin. "Indeed so sensitive to vitamin A deficiency is the cerebrospinal pressure that Sorensen (12) and others (1954) suggest it may be used as a guide to the onset of deficiency."

The same conclusion is reached by Rokkones (13) who in 1955 published studies on the offspring of vitamin A deficient rats. He concludes that "A rise in the cerebrospinal pressure appears to be the most characteristic and sensible symptom of the disease. It is demonstrable already before the occurrence of hydrocephalus and before the animals show visible symptoms."

The results of these recent animal experiments account very well for the findings in the vitamin deficient infants, for it would be impossible to explain the rapid disappearance of symptoms and signs of increased cerebrospinal fluid pressure when vitamin A was given, if they were due entirely to defective bone formation.

INCREASED INTRACRANIAL PRESSURE AND ACUTE HYPERVITAMINOSIS A

In 1951 Julien Marie and Georges See (14) published a report of three infants who, after the ingestion of a single huge dose of vitamins A and D, responded after twelve hours with extreme bulging of the fontanelle, lasting twelve to twenty-four hours. The vitamins were in the form of a preparation known as Vitadone forte which contained 350,000 units of vitamin A and 300,000 units of vitamin D. The infants twelve to twenty-four hours after ingestion usually vomited and showed restlessness, discomfort, insomnia or drowsiness. Believing that these symptoms were due to the vitamin A and not to vitamin D, authors gave a number of infants large doses of vitamin A alone (350,000 units) and were

able to reproduce this transitory bulging fontanelle in three of six infants. Spinal tap in these cases showed an increase in fluid pressure. The cytology and chemistry of the fluid was normal. Blood pressure remained normal. Vitamin A content of the blood rose to many times the normal but then fell rapidly as the symptoms disappeared. No vitamin A was demonstrable in the spinal fluid. They were unable to produce the syndrome when synthetic vitamin A was used instead of the natural vitamin, nor could they reproduce it with the subcutaneous injection of 60,000–90,000 units of natural vitamin A. The authors were able to reproduce the bulging fontanelle in some of the young puppies used as experimental animals.

Their conclusion reads (15) "Our clinical observations and our work on infants and animals convinces us that the acute hydrocephalus, with intensive bulge of the fontanelle, produced by the rapid absorption of vitamin A is a transitory and harmless disorder in both its immediate and its remote prognosis."

In the past five years this syndrome in infants has been reported by numerous authors from different countries. In one case it resulted from a preparation of vitamin A used as nose drops.

In this connection it is of interest to note that, especially in the Arctic regions, acute vitamin A poisoning in adults is not unknown. It occurs from ingestion of seal or polar bear liver which contains enormous quantities of the vitamin. One of the chief complaints in this illness is particularly violent headache accompanied by dizziness and somnolence. As pointed out by Knudsen and Rothman, (16) these symptoms may very well be due to increased intracranial pressure.

In contradistinction to acute poisoning from single large doses of vitamin A, there are now many reports of chronic hypervitaminosis A due to the prolonged use of excessive amounts of the vitamin. Such cases usually reveal symptoms due to lesions in the osseous system and only very rarely present neurological manifestations. However, two cases have been reported where infants with chronic poisoning showed signs of increased intracranial pressure (Gribetz (17) and Arena (18)).

A curious case was reported by Ehrengut (19) in 1955:

A five month old infant who had been on a soy bean milk without vitamin supplement since the age of three weeks developed keratomalacia, pustular skin lesions and gynecomastia. Avitaminosis A was diagnosed and 187,000 units of vitamin A was given in two days. This was followed by the appearance of very marked bulging of the fontanelle. Spinal fluid was found to be normal but under very high pressure. Vitamin A was stopped and the fontanelle returned to normal. Several days later 44,000 units of vitamin A was given by mouth with return of the bulging fontanelle. When the vitamin was discontinued the fontanelle again returned to normal in two days. The author considers the case one of acute hypervitaminosis A (Marie-See Syndrome) resulting from excessive intake of vitamin in attempting to cure symptoms due to prolonged vitamin A deficiency.

Just as we have seen hydrocephalus produced experimentally in litters of animals kept on a vitamin A deficient diet, so, curiously enough, hydrocephalus has also been produced in the offspring of rats fed *excessive* amounts of the same

vitamin (Cohlan-20). In other words hydrocephalus may result in experimental animals and in human infants both in *hypo* and *hypervitaminosis A*.

Apparently this paradox may also be found in symptoms referable to the eyes of pigeons. Under the title "Avitaminose et hypervitaminose A du pigeon. Identité de leur séméiologie oculaire," Mouriquand (21) and his collaborators point out that the pigeon needs very little vitamin A in contradistinction to the rat, which very early shows signs of deprivation. In pigeons even as long as 300 or 400 days of deprivation, symptoms disappear very quickly when small doses are given. Both the loss of periocular feathers, resulting in the so-called "spectacle" appearance and changes in the eye itself occur in both *hypo* and *hypervitaminosis A*.

DISCUSSION

From the foregoing I believe we can definitely state that increased cerebrospinal pressure may occur both in overdosage as well as deficiency of vitamin A in infants and young animals. There is apparently in both conditions a defect in the production or absorption of cerebrospinal fluid. There are more published reports of human infants with bulging fontanelles due to acute hypervitaminosis A than to vitamin A deficiency. Most, though not all have been on some form of soy bean preparation. Mellanby (21) in 1931 postulated from work on puppies that vitamin A might be important in preventing damage to the nervous system by toxins derived from cereal grains fed to the animals. One can only speculate as to whether such a relationship might exist in some of the human infants deprived of vitamin A and fed on preparations made from soy bean.

That the ingestion of certain chemical substances may result in increased cerebrospinal pressure is emphasized by the recent observation of Gellis that "A bulging fontanelle may accompany antibiotic therapy. In these instances the bulging fontanelle was apparently directly related to antibiotic therapy and not to infection present; subsequently when the same children were tested with the same antibiotics at times when they were free of infection, the fontanelle could again be made to bulge during course of therapy and would promptly subside within twenty-four hours after antibiotics were discontinued. This has been seen most frequently with aureomycin." (23)

It is also strange that in reports in vitamin A deficient children in China, where this condition is common, no mention is made of hydrocephalus as one of its symptoms. Thus Sweet and K'Ang (24), in 1935 published a clinical and anatomical study of avitaminosis A in 203 Chinese infants, with seventeen autopsies and twenty-two biopsies. No mention is made of the finding of hydrocephalus either clinically or at post-mortem. However, the authors do mention headache as a late symptom in cases with severe ocular lesions. The headache was "Sharp, piercing and difficult to control." There were also convulsions in four cases but no lesions were found in any of the cases to explain them.

It remains hard to explain why we see hydrocephalus in vitamin A deficiency in America and not in China where dietary deficiency is so widespread. The possibility of a second factor must be kept in mind.

Bicknell and Prescott (25) in their book on "The Vitamins in Medicine" make this relevant comment. "In man no neurological symptoms are generally associated with those conditions, such as keratomalacia, where they would be expected if the central nervous system were affected by vitamin A. There is however, the possibility that in man, as in animals, the degeneration gives such tardy symptoms that they seldom occur before the deficiency has been remedied or death occurs, unless degeneration is accompanied by a second deficiency."

To sum up we can only say that up to the present time we have no adequate explanation for our clinical findings in infants. Symptoms referable to the nervous system in vitamin A deficiency are more common than has been previously believed and the pediatrician should keep this condition in mind when signs of unexplained acute hydrocephalus are encountered.

The problem of the cause of hydrocephalus in hypo and hypervitaminosis A is a challenging one and its solution awaits further clinical and laboratory investigation.

ACKNOWLEDGMENT

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THE DIAGNOSIS OF ACUTE APPENDICITIS—A REAFFIRMATION OF BASIC SURGICAL PRINCIPLES

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With progressive widening of the surgical horizon due to improved techniques and development of special surgical skills, the surgical literature has become almost completely preoccupied with many esoteric problems of relatively low frequency in the general surgical population. As one result, young surgeons in training tend to negate old, well established principles of management in many of the common surgical problems. More particularly in reference to acute appendicitis it is important to make a plea now for the 'non-operating surgeon (1)'. That it is easy to remove the appendix is no argument against invoking precise diagnosis and indications; similarly, it has become almost as easy to remove a stomach or to stretch a mitral valve. One wonders whether large series of cases reflect this facility rather than prime indication and judgment.—What is the case for the 'lily-white appendix?'

Let us examine the often repeated argument that there is no harm in removing the appendix which is without disease. To be sure, statistics can be cited pointing to the almost infinitesimal operative mortality following such a procedure. However, this would hardly reflect the true significance of the problem. Firstly, it is self-evident that appendectomy performed in the presence of disease other than acute appendicitis does not constitute proper therapy for the underlying undiagnosed condition. Not only has the patient been subjected to an unnecessary operation, but what is much more serious, the underlying disease (pneumonia, poliomyelitis, diabetic acidosis, renal colic, etc.) may be aggravated by the disturbed body physiology consequent to anesthesia and appendectomy. Moreover, prompt recognition and proper therapy for the underlying disease may be further delayed by the masking effects of nausea, vomiting, and abdominal pain incident to the laparotomy. The following sequence of events occurred recently in a tragic case in a nearby community. A 16 year old young woman with vague abdominal pain was considered to have acute appendicitis and was subjected to appendectomy within 2 hours of the onset of her symptoms. The pre-operative urine analysis had been omitted because the voided specimen was inadvertently mixed with the stool. It was not until the second preoperative day that the diagnosis of severe diabetic acidosis was recognized by a visiting consultant. Despite energetic measures, coma and death ensued. Certainly, such a tragedy, rare perhaps but inexcusable, is poignant evidence against the loose philosophy that appendectomy is harmless.

Laparotomy continues to be associated with an irreducible morbidity and

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mortality despite modern advances in surgical technique and postoperative care. Several years ago an indelible impression was made on one of us whose patient succumbed to a fatal pulmonary embolus following an unneeded appendectomy. Incisional hernia and intestinal obstruction months or years following appendectomy represent a large unmeasured source of morbidity.

As surgeons we must be ever mindful of the socio-economic implications of appendectomy. Cost to the patient, separation from the family, time lost from work and school are a few implications of every operation to say nothing about the utilization of precious hospital beds. Blue Shield rates and those of other health and accident plans must reflect the indiscriminate use of this high-frequency procedure as a hidden unnecessary cost.

Perhaps it is the growing recent lay and professional recognition of these facts that has prompted the American College of Surgeons to recommend that accredited hospitals form tissue committees whose functions are to audit the work of each individual surgeon. The indications for appendectomy are properly used as a yardstick in evaluating surgical judgment. This represents self-discipline at its best, and all that is required is that the data on each chart warrant a pre-operative diagnosis of acute appendicitis. It is agreed that in the best of hands an error of 15-20% may be expected, and there are many patients in whom other conditions will be indistinguishable from acute appendicitis. This comes to the point of the issue, as stated by Thieme (2), who advises that in a large group of doubtful cases it would be perfectly safe to delay appendectomy for further observation rather than adopt the policy of 'when in doubt, take it out.' If it can be shown that close observation under controlled conditions in a hospital does not increase morbidity or mortality, the number of unwarranted operations with attendant undesirable sequelae may be significantly decreased.

No one gainsays the fact that there is a continuing mortality and morbidity in acute appendicitis. Boyce (3) cites figures to show that the death rate of acute appendicitis in the United States is 1.7 per 100,000, that is, 2600 deaths, for the year 1952, and attributes this in large part to so-called atypical cases. Everyone grants that the diagnosis of acute appendicitis may be extremely difficult, despite the fact that we often presume to make it on short notice with little deliberation. It would be reasonable to presume that every patient with abdominal pain who warrants surgical consultation should warrant observation in a hospital. This could be accepted better by family physicians and the public at large if it did not imply in every instance appendectomy as well. With this reassurance, patients with abdominal pain would accept hospital observation. This might well facilitate the recognition of so-called atypical manifestations of the disease overlooked not infrequently at home.

The in-hospital observation of a patient with abdominal pain does not imply a conservative, dilatory or procrastinating attitude. We do recognize appendicitis as a serious and relatively urgent disease. But, too often in the past a single tragic experience of family physicians, surgeons, and even family groups has influenced surgeons towards a nondiscriminating, wholesale attack on all persons with abdominal pain to eliminate any chance of error. Actually, today the dangers

of appendicitis have carried a 'fear-value' beyond its true nature with modern-day antibiotics and better understanding of the disease. Too often inordinate extraneous pressures work on the surgeon due to this fear engendered by the parents and family.

In few other medical situations are we called upon to make a diagnosis at the time of the initial examination, before all the evidence is available, and before the disease has existed long enough to manifest physical findings. Unwittingly, how often have we as surgeons aggravated this fear in a dramatic overstatement by boasting that we removed the appendix in the nick of time just before rupture.

What precisely should be involved in this concept of in-hospital observation, which we feel is radical only in that we assume the responsibility, and do not void it by unnecessary surgery? Firstly, all patients with a good history of epigastric or midabdominal pain that shifts to the right lower quadrant, with one of the equivalents of anorexia, nausea or vomiting, who have on physical examination local tenderness in the right lower quadrant with muscle guarding, are operated upon without unnecessary delay after blood count and urinalysis have been performed. The local physical findings cannot be disregarded despite a normal blood count. In brief, once a clinical diagnosis of acute appendicitis has been made there is no delay or observation. However, and this is to the point of this paper, in a significant percentage of cases there is a history of abdominal pain with few or no physical findings to point precisely to a diagnosis. After the initial history and physical examination are done without urgency, a deliberate workup is initiated. This includes the usual laboratory studies and the use of other ancillary laboratory services and consultants as indicated.

All surgeons with experience have developed almost intuitive aids in history-taking. As a rule, the symptoms of anorexia are significant and one does not like to operate upon a patient who is hungry. Yet, there are occasional exceptions to this rule in the presence of good local physical findings. Keyes (4, 5) has repeatedly stressed the significance of the so-called 'gas stoppage' sensation in the history—a bowel urge associated with abdominal pain which persists despite defecation. It would seem hazardous to venture an early diagnosis of acute appendicitis by history alone before physical findings become manifest. Diarrhea, unfortunately, means 'no appendicitis' to many physicians, but not infrequently reflects pelvic appendicitis which may not be suspected on examination of the abdomen, and may only be diagnosed by repeated rectal examinations over a period of time. Too often points of history are obtained after the fact in cases which have been done urgently with negative findings. Unfortunately, residents, interns and medical students speak of a surgical history-taking as a 5-minute rapid survey in contrast to medical history-taking which often elicits much valuable information. This applies also to the physical examination which often exposes only the lower abdomen to the surgeon's hands, again with the excuse of urgency. A complete physical survey, including pelvic and rectal examinations, inexcusably often does not appear on the charts of many patients who have had an urgent normal appendix removed.

Once the complete history, physical and initial laboratory work have been

completed and the diagnosis is still uncertain, other aids can be employed. A plain film of the abdomen in persons over 40 years of age may reveal a distended cecum secondary to an obstructed left colon as a cause of the right lower quadrant pain. Abnormal findings in the urine may invite a cystoscopic examination or an intravenous pyelogram. X-ray of the chest and electrocardiogram may be indicated in the elderly. A serum amylase may indicate an unsuspected pancreatitis. A gynecologic consultation may obviate surgery for pelvic inflammatory disease, for pain during the catamenia or 'mittelschmerz.' In a series reported by A. A. Levi of 242 women in the menstrual age of 11 to 50, 24 were operated upon during their period and only 9 had acute appendicitis (6). It is well known that there are many physiologic changes taking place in the pelvic organs during this time, such as reflux of blood through a tube, which could account for local pain and tenderness in the absence of appendicitis. In each of the trimesters of pregnancy there are reasons for abdominal pain which might mimic acute appendicitis. Boyce (3) showed that appendicitis during pregnancy is infrequent. Actually, in a series of 7613 cases of acute appendicitis only 52 cases were found in pregnant women. This is not to deprecate the seriousness of appendicitis as a complication of pregnancy, but in these cases 4-6-8 hours' observation and consultation with the obstetrician may be invaluable, bearing in mind the changes in the position of the appendix as the uterus enlarges.

Certainly, the workup should be directed, and not a shotgun, cover-all, expensive exercise. This takes time, but the patient is still kept in focus and repeated examinations are performed, including pelvic and rectal examinations, at intervals no greater than 4-6 hours until a proper diagnosis can be established. Once good local physical findings are evident, surgery is scheduled and, as a rule, only 6-12 hours of progressive pathology elapses with little or no harm to the patient. Contrariwise, many patients with nondescript abdominal pains are discharged within 24-48 hours. With this kind of observation the so-called 'atypical cases' declare themselves if the observer is alert to the possibility of retrocecal, retroileal, and pelvic appendicitis. Certainly, in infants and in the aged an even more aggressive concern may shorten the period of observation before exploration because of manifest difficulty in evaluating physical findings at the two polls of life. It takes extreme patience and intimate cooperation with the pediatrician to evaluate abdominal pain and physical findings in the abdomen of an infant. In the aged, one does not insist on muscle rigidity and the good localization of physical signs present in younger age groups, once other causes of abdominal pain have been excluded by proper workup.

Observation is carried out with the restriction of oral intake and without antibiotics which conceivably could mask the signs and symptoms of the prevailing pathology. Not infrequently patients under observation will be proven to have other acute intra-abdominal pathology other than acute appendicitis, which may require urgent surgery for which better preparation can be accomplished, and a more proper surgical approach utilized (acute diverticulitis, acute cholecystitis, perforated ulcer, etc.).

Would this policy of controlled observation lead to increased morbidity or

TABLE I

Mesenteric adenitis.....	11
Ruptured follicle cyst of ovary.....	5
Gangrenous appendices epiploicae.....	1
Infarcted leiomyoma uteri.....	1
Acute salpingitis.....	1

TABLE II

	Total Cases	Average Hospital Stay (Days)	Per Cent Morbidity	Per Cent Perforation
Operation immediately.....	167	7.3	2%	20%
Operation after observation.....	21	8.9*	3%	8%

* Includes period of observation.

mortality in the management of acute appendicitis? It is with this in mind that we have reviewed our experience over a 4-year period. This study consists of analysis of 188 cases operated upon by the authors from January 1, 1953 to December 31, 1956, inclusive, with the pre-operative diagnosis of acute appendicitis. In 153 of these the pathologist's report was acute appendicitis. This constitutes a pathologic diagnostic accuracy of 81.4%. In an additional 19 cases (10.1%) other significant intra-abdominal pathology was found. The diagnoses in these cases are listed in Table I. In the remaining 16 cases no intra-abdominal disease was found at laparotomy and the pathology report was normal appendix. This constitutes a diagnostic error of 8.5%. If we exclude these 16 cases from the total, there are 172 cases of 91.5% in which either acute appendicitis or other significant intra-abdominal pathology was found.

In 167 cases the diagnosis of acute appendicitis was evident on hospital admission or shortly thereafter, and laparotomy was carried out without delay. In the remaining 21 cases a period of controlled hospital observation of 6 hours or longer was instituted prior to the decision for surgical intervention. Analysis of these 21 cases compared with the 167 cases in which operation was performed immediately upon admission revealed that in no way did the "delay" in surgery after a period of controlled observation contribute significantly to increased hospital stay, increased morbidity or percentage of perforations (Table II).

It is interesting to note that the higher percentage of perforations present in the patients operated upon immediately might reflect an over-long period of delay in the home without proper observation.

It was most interesting to observe that during the period of study (1953-1956) 253 additional patients were discharged without operation after being hospitalized for from 1-3 days for observation of possible acute appendicitis. After the observation period, when further diagnostic studies could be obtained, more precise diagnoses were revealed. These included pelvic and renal disease, gastroenteritis, sigmoid diverticulitis, hepatitis, infectious mononucleosis, poliomyelitis, and pneumonia. In a number of instances, no diagnosis could be made

after symptoms had completely subsided and all diagnostic studies were negative. These patients were subjected to close followup for a period of weeks and months without any untoward results. They represent an incalculable salvage in terms of expense, disruption of family life, morbidity, and late complications from unnecessary surgical procedure. These non-operative cases, unfortunately, are rarely reported in surgical literature. A resident in surgery is always proud to report the number of surgical procedures he has performed during his residency. Should he not also report with pride the number of cases of abdominal pain which he has carefully observed, properly diagnosed, and referred for proper non-operative management? Charles W. Mayo (7), in a recent editorial on surgical judgment, concluded by saying that his surgical approach to a patient is as follows: "Can I justifiably get this person out of having an operation not into having one? The surgeon whom I would select to treat my family and me must first know when not to cut, when and where to cut, how to cut, and when to stop cutting." Such an expression reflects our attitude as related to the problem of appendicitis.

CONCLUSIONS

1. The degree of accuracy in the diagnosis of acute appendicitis can be enhanced significantly by controlled in-hospital observation of patients with abdominal pain.
2. The alarming incidence of unnecessary appendectomy can be reduced by such a program.
3. Such a program did not lead to increased morbidity in a series of patients so managed.
4. The positive results of such a program are reflected by the large number of patients spared surgery with incalculable savings economically and socially.
5. This kind of management restores the diagnosis of appendicitis as a proper discipline in general surgery.

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THE SIGNIFICANCE OF SERUM BILIRUBIN AND SERUM ALKALINE PHOSPHATASE IN CHLORPROMAZINE THERAPY

A STATISTICAL STUDY OF 1215 PATIENTS

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INTRODUCTION

In large series of patients treated with chlorpromazine, the incidence of jaundice has varied, from one instance in 506 cases (1), five in 800 (2), and 13 in 3014 cases (0.43 per cent) (3). In one smaller series the incidence has been slightly higher; three in 71 patients (4). Various combinations of liver function tests have been tried to detect impending jaundice during chlorpromazine therapy.

It is the purpose of this paper to attempt an evaluation of the relationship between serum alkaline phosphatase and any rise in serum bilirubin during treatment with chlorpromazine and to present statistical conclusions based on a large number of determinations.

Results of other liver function tests in random or serial observations have been inconclusive. Which test or tests should be selected for the quasi-obstructive type of jaundice (5), is not yet standardized. We may assume that chlorpromazine will continue in use in both psychiatric and non-psychiatric conditions and will require laboratory checks for toxic complications.

Even a recent comprehensive discussion of the chemical evaluation of liver function tests (6) serves only as a general guide. In studies of liver toxicity due to chlorpromazine the cephalin flocculation, thymol turbidity and zinc sulphate procedures have shown no consistent changes (2, 7, 8), although slight variations in cephalin-flocculation values were noted by Lehman and Hanrahan (4) in half of their 71 cases. Among five jaundiced cases due to chlorpromazine (7), there were negligible or no alterations of the total protein and albumin-globulin ratios. Cholesterol and cholesterol esters were found to be normal during jaundice in one investigation (8), but total serum cholesterol was elevated to 600–700 mgm/per cent in one of five cases in another series (7), and in one of the three cases of a third study (9). In another report of non-jaundiced patients, ten per cent showed abnormal bromsulphthalein excretion during treatment (10).

A battery of liver function tests performed by Cohen and Archer before and during chlorpromazine treatment of 70 cases showed no significant alteration (2). Their studies included serum bilirubin, serum alkaline phosphatase, total cholesterol, thymol turbidity, albumin-globulin ratio, prothrombin time and

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bromsulphthalein excretion. Similarly, results with a set of liver function tests were not of clinical value in the 33 cases of Kinross-Wright (11).

METHODS

During an 18-month survey of 3014 mental patients on chlorpromazine (3), we found occasional high values of serum alkaline phosphatase, using the Bodansky method. Shortly after beginning our phosphatase studies, Doctor Harry Goldenberg, Chief Chemist of the Hillside Hospital, Glen Oaks, N. Y., made available to us, prior to publication, his rapid and accurate method for serum alkaline phosphatase (12).

Utilizing Goldenberg's procedure, 1215 new cases admitted to chlorpromazine therapy were studied during the six-month period beginning January, 1956. Simultaneous serum total bilirubin and serum alkaline phosphatase values were determined. Patients were screened during the week before treatment for extraneous liver or skeletal disorders. During treatment, from one to eight bilirubin and phosphatase tests were performed on each of the 1215 patients. A total of 2077 bilirubin and 1978 alkaline phosphatase determinations were made. Blood samples were taken during the first three weeks of treatment and repeated as often as practical at three or four week intervals. When elevated values were found, tests were usually repeated at weekly intervals.

It was considered advisable to make a statistical study of the accumulated data to establish the normal values for our own hospital population. This was preferable to accepting published normal values derived from a control group of differing compositions in age, mental and/or physical status. The statistica

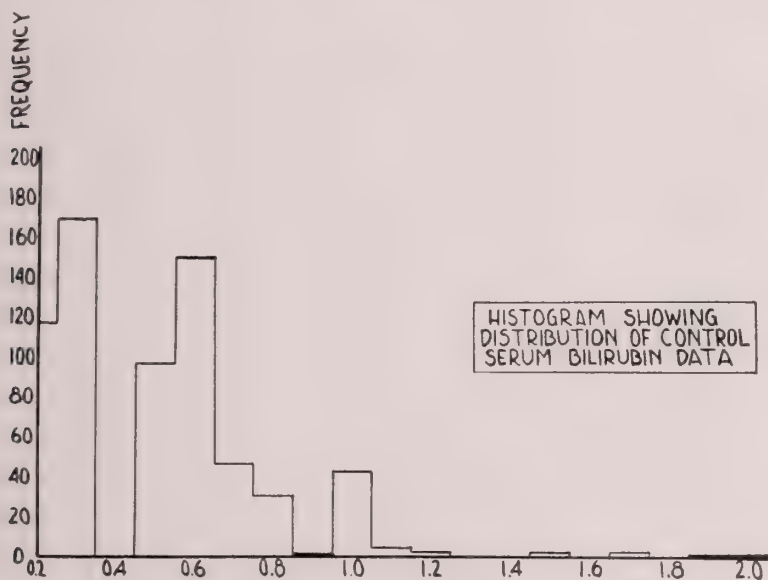


FIG. 1. Distribution of total serum bilirubin, mgm. per 100 ml., among 661 pre-treatment controls.

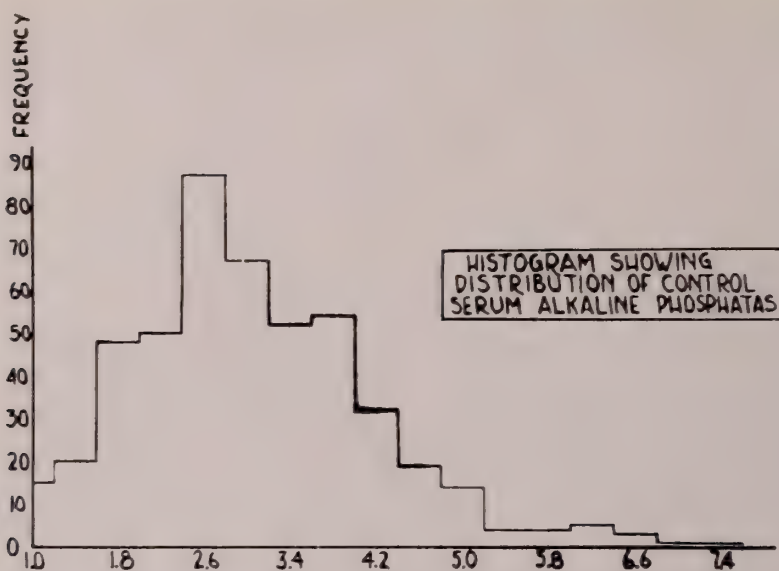


FIG. 2. Distribution of serum alkaline phosphatase (Goldenberg), units per 100 ml., among 476 pre-treatment controls.

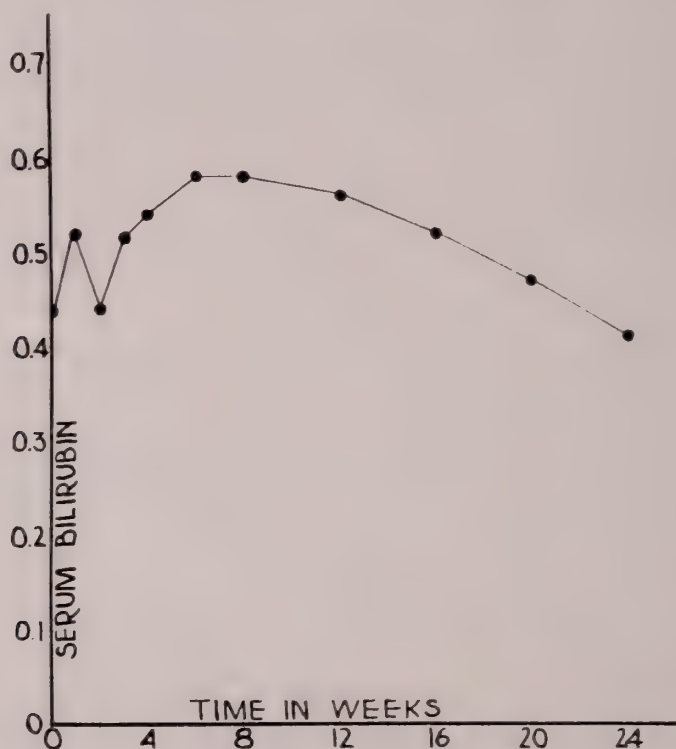


FIG. 3. Mean values of total serum bilirubin, mgm. per 100 ml., among 1215 treated patients.

significance of the relationship between serum alkaline phosphatase and the serum bilirubin was studied. Computations included the mean values, the variances, standard deviations, standard error of the mean and the ratio of the differences between the means to the standard error. Standard statistical techniques were used throughout this study (13). The rationale for selecting these parameters is discussed elsewhere (14).

RESULTS

Using our screened controls among patients scheduled for chlorpromazine therapy during the following week, we established the values for normal serum bilirubin. Among 661 such determinations, concentrations ranged from 0.2 mgm. per 100 ml. to as high as 2.0 mgm. per 100 ml. with a mean value of 0.44 mgm. per 100 ml. The distribution curve was skewed; 90 per cent fell between 0.2 and 1.0 mgm. per 100 ml. (Fig. 1). The variance was 0.067 and the standard deviation 0.26. The upper limit of our controls was established as 1.0 mgm. per 100 ml. as compared to 0.8 mgm. per 100 ml. of Cantarow and Trumper (15). It is of interest to note that our figure for the upper limit coincides with the carefully controlled statistical study of serum bilirubin values in 720 healthy, adult males reported by Zieve and Hill.

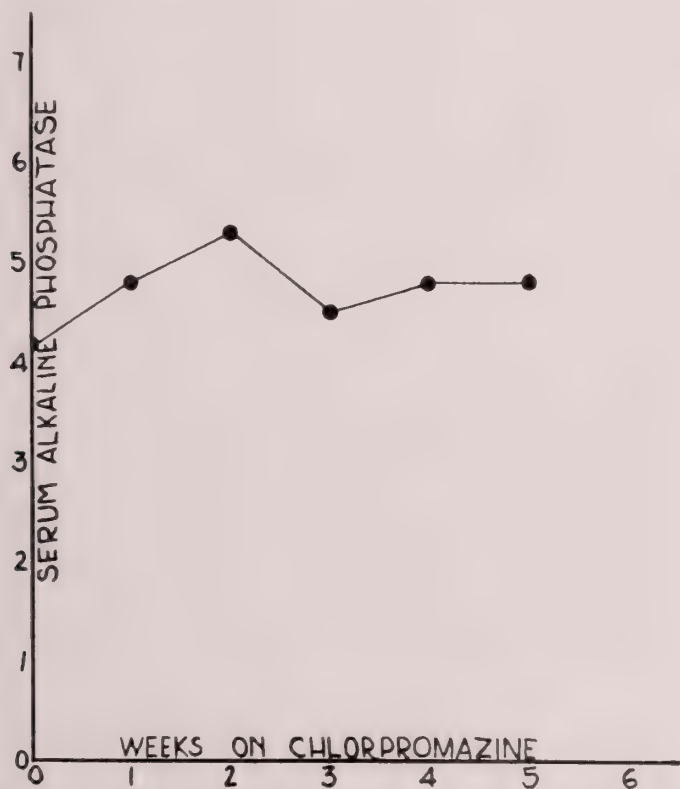


FIG. 4. Mean values of serum alkaline phosphatase (Goldenberg), units per 100 ml., among 1215 treated patients.

Among 476 serum alkaline phosphatase control determinations, using the Goldenberg procedure, a similarly skewed distribution of values was noted (Fig. 2). The mean value was 3.05 units per 100 ml. with a variance of 1.25 units per 100 ml. and a standard deviation of 1.12 units per ml. Utilizing plus or minus three standard deviation units, the upper limit for normal alkaline phosphatase was found to be 6 units per 100 ml. This contrasts with the findings in Goldenberg's laboratory (17) for an upper normal of 3.9 units per 100 ml. This investigator used a considerably smaller sample size, of differing composition.

During the course of treatment minor changes were found in the mean values for both serum bilirubin and alkaline phosphatase as summarized in Figures 3 and 4. The ratios of the difference between control and treatment means to the standard error of the differences were computed. We found no statistically significant differences between the control and treated groups even though the high values of the seven cases with jaundice occurring among the 1215 patients were also included.

Another statistical approach to the relationship between the serum bilirubin and alkaline phosphatase was made. We selected all those subjects under treatment who showed values of serum bilirubin above the normal limit of 1 mgm. per 100 ml. but who showed no evidence of clinical jaundice. The mean values

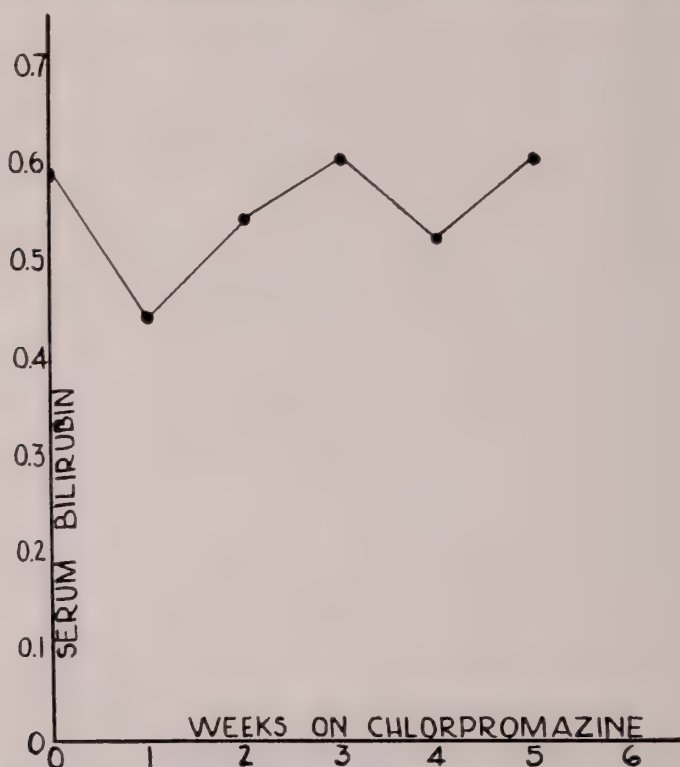


FIG. 5. Mean values for total serum bilirubin mgm. per 100 ml., for patients who had values above 1 mgm. one or more times during treatment.

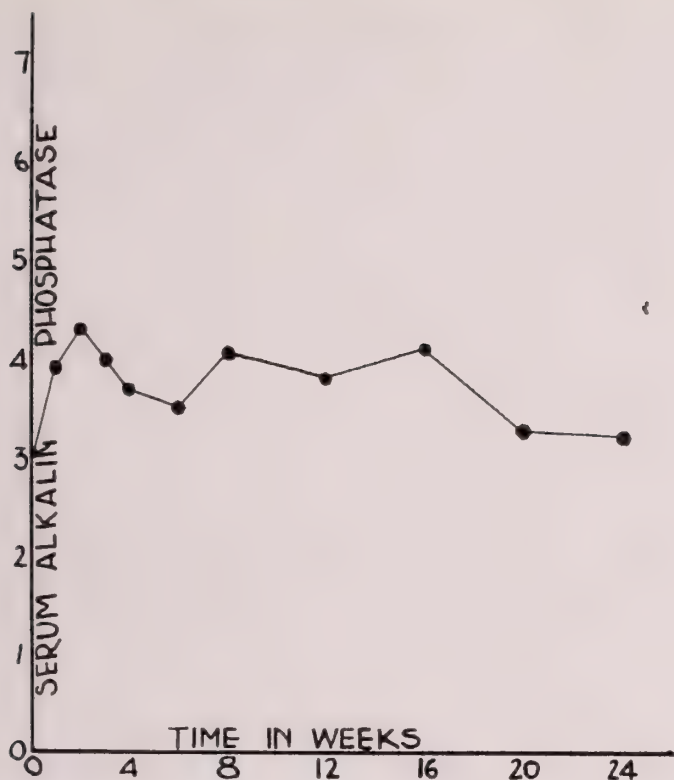


FIG. 6. Mean values for serum alkaline phosphatase (Goldenberg), units per 100 ml. for patients who had values above 1 mgm. per 100 ml. of serum bilirubin. (See Fig. 5).

at the stated weekly intervals of such single or multiple determinations are shown in Figures 5 and 6. This group, with so-called "latent icterus," transient or sustained, showed a mean total bilirubin value of 0.57 mgm. per 100 ml. compared with 0.44 mgm. per 100 ml. among the pretreatment controls. This difference, again, was not statistically significant. The changes in mean serum alkaline phosphatase levels in this selected group were correspondingly insignificant.

The question of any correlation between serum bilirubin and serum alkaline phosphatase in chlorpromazine jaundice was next studied. The survey of the 3014 subjects on chlorpromazine during an 18-month period (3), disclosed 13 cases of clinical jaundice whose serum bilirubin ranged from 4.2 mgm. per 100 ml. to as high as 36 mgm. per 100 ml. on repeated determinations. Figure 7 is a scatter diagram showing serum bilirubin and serum alkaline phosphatase values for simultaneous determinations on the 13 subjects in this group. The correlation coefficient was computed to be 0.51, which is rather low. A perfect correlation would have a value of 1.0. In any unrelated large series of measurements, values approximating 0.2 or 0.3 may be found.

Once the clinical icterus was established in the 13 cases, they all showed alkaline phosphatase values consistently above eight units on one or more deter-

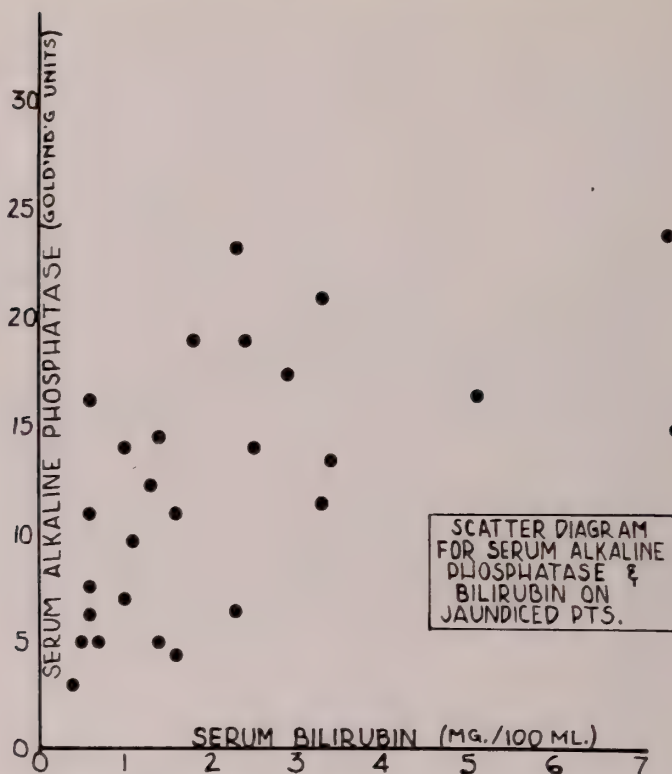


FIG. 7. Scatter values for simultaneous determinations of serum bilirubin and alkaline phosphatase in 13 jaundiced cases among 3014 chlorpromazine-treated patients.

minations. Nevertheless a clinically useful correlation coefficient, enabling a prediction of one value from the other, was not found.

DISCUSSION

One of the greatest obstacles to a clear evaluation of an accumulated lot of biochemical measurements is the deficient application of statistical methods. Another pitfall is the tendency to adopt a numerically small sample of control data obtained from a dissimilar group as a permanent parameter. The faulty conclusions of some investigators concerning normal and abnormal values are often due to failure to recognize the quantitative interdependence of inherently variable biochemical factors. This is especially so when a part of all these factors are uncontrollable. The variations among sizes of samples among different laboratories; the differences in biochemical composition of patient material; modifications in procedures, differences in technicians—all these contribute to the nonuniformity of normal and abnormal means and ranges. They account for striking deviations in data from different studies which, on statistical analysis, can be shown to be more apparent than real.

Zieve and Hill's studies (16) have clearly indicated the need for statistical interpretation of normal and abnormal biochemical values. They performed a

group of the commoner liver function tests on 720 selected healthy males and statistically scrutinized the findings. These authors admirably discuss the dangers of illogical deductions from any series of inherently variable measurements. They state, "on the basis of experience, the qualified physician attaches variable weight to findings, ignoring some, to combine them into a formula to predict the disease state. He applies the concept of multiple correlation and regression in a nonqualitative way." We concur in their opinion that simple statistical techniques are not applied frequently enough to multivariate biochemical data. Generalizations from random samples or random high values must be avoided when going from controlled data (in one series) to uncontrolled data in subsequent long-term biochemical procedural routines.

From the viewpoint of good statistical practice, the size of our sample data for bilirubin and phosphatase was adequate. Our base line was the control group of arbitrary "normal" patients before they were placed on chlorpromazine therapy. This was a statistically select group, being derived from various ages and sexes, all with a background of mental disease, functional and or organic, of varying duration. These factors remained constant during the experiment so that they were without effect. Since a large percentage, 35 per cent, were over 60 years of age, their normal biochemical values differed somewhat from that of the total group.

The need for establishing biochemical standards in one's own laboratory rather than adopting published values may be illustrated with the Goldenberg alkaline phosphatase technique. Using limits found by Goldenberg for normal, (3.9 units), and elevated serum alkaline phosphatase, before or during chlorpromazine treatment, we analyzed the collected data of our 1215 patients (3). We determined the incidence of phosphatase values in three ranges since rises to 5.5 units during chlorpromazine treatment were often found by Goldenberg. Between 3.9 and 5.5 units, the incidence in our own material for controls and treated cases were respectively, 13.0 per cent and 14.7 per cent, a negligible difference. In the second range, from 5.5 to 8 units, our treated cases showed an incidence of 7.3 per cent compared with 3.1 per cent among controls. Pronouncedly abnormal elevations of alkaline phosphatase, above 8 units, had a frequency, in a treated group, which included 13 jaundiced cases, of 4.8 per cent as contrasted with 0.2 per cent in controls. This is not a pronounced deviation percentage-wise, as applied to 1215 cases.

Direct comparisons of the frequency obtained between control and treated groups were possibly modified by the size of our samples. There were 476 control measurements as compared to 1978 phosphatase determinations during therapy. In any skewed distributions, the larger the sample, the more likely will random high values be encountered, i.e., the "tail" of the curve is further extended.

As the bilirubin-phosphatase correlation among 13 jaundiced cases was found to be only 0.51, the interdependence of these two variables was statistically low. No statistical studies have been published of the effects of chlorpromazine on thymol turbidity, cephalin-flocculation, cholesterol or other common liver func-

tion tests. Nevertheless, it appears that the serum alkaline phosphatase test has no greater diagnostic import than any of the above named procedures. It remains to be seen whether the serum transaminase test which determines damage to the liver and not its function, may prove more valuable in detecting early toxicity in chlorpromazine therapy.

The most consistent test for the early detection of chlorpromazine jaundice is the serum bilirubin determination. Even this bellwether for jaundice is influenced by the odd behavior of serial bilirubin values in some of our cases as well as in those of other observers. This is, that in the "abnormal" range between 1.5 to 4 mgms. per 100 ml., a progressive rise, on continued treatment, to values consistent with clinical jaundice, was not the rule. Such subicteric elevations of serum bilirubin (from 1 to 3 mgm. per 100 ml.) would occasionally regress to normal during uninterrupted treatment, thereby vitiating the prognostic significance of values slightly above normal.

CONCLUSIONS

1. During a 6-month period of chlorpromazine treatment, 1215 mental patients received simultaneous serial serum total bilirubin and serum alkaline phosphatase determinations.

2. Control values were determined utilizing part of these patients during the week before treatment.

3. A statistical analysis was made, using the standard computations of mean values, variances, standard deviations, standard error of the mean and the ratio of the differences between the means to the standard error.

4. There were no significant differences between the mean serum total bilirubin value and the mean serum alkaline phosphatase value in controls and in treated cases.

5. Among 13 cases of jaundice occurring in 3014 chlorpromazine treated patients, the positive correlation coefficient between serum bilirubin and alkaline phosphatase was 0.51. This is slightly more than that which would be due to chance.

6. The serum total bilirubin in the zone of doubtful abnormality above 1 mgm. per 100 ml., corresponding to latent icterus, showed a mean of 0.57 mgm. per 100 ml. as compared with 0.44 per 100 ml. among pretreatment controls; this difference was not statistically significant.

7. A review of reported alterations of liver function tests (excluding serum bilirubin) during chlorpromazine treatment was made. The same lack of prognostic significance of such tests applied to the serum alkaline phosphatase determination.

8. The only useful but not constantly applicable indication of impending or early chlorpromazine-induced jaundice is the rise in the serum bilirubin level.

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APPLICATION OF THIN SECTIONS TO THE PROBLEMS OF RENAL PATHOLOGY*

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Microscopic study of the normal and particularly of the abnormal kidney is greatly facilitated by the use of thin sections. The definition of what constitutes a "thin section" has changed a good deal in the last few years. Only recently, Bell (1) considered thickness of 5 micra, or less, as satisfactory. Jones (2) and Churg and Grishman (3) found that reduction to 2 micra resulted in much clearer visualization of pathologic changes in the glomeruli. Even this may not be thin enough to reveal the fine details of glomerular inflammation. Until recently, 2 micra was about the practical limit obtainable with paraffin embedding and conventional microtomes. Development of special microtomes (4, 5) and special embedding methods, (6, 7) for electron microscopy made it possible to cut sections under $\frac{1}{10}$ micron. These same or similar methods can be used to obtain serial sections 0.5–1 micron thick and sufficiently large to contain a number of glomeruli. Such sections can be stained by appropriate methods, or can be studied unstained under the phase microscope. Details of embedding, sectioning and staining have been given elsewhere (8). Because of their thinness, these sections permit full utilization of the resolving power of oil immersion objectives. They afford an unsurpassed clarity of detail and sharp definition at magnifications up to 2000 diameters. This is only a step removed from the lower range of the electron microscope.

Recent electron microscopic studies have significantly contributed to the knowledge of normal glomerular architecture. There have been only a few studies in the field of renal pathology, partly because of its extreme complexity (9), partly because of the difficulty of correlating the familiar images of disease processes in stained preparations under comparatively low magnification, with the black and white pictures, high magnification and limited fields of the electron microscope. Stained thin sections provide direct means for clarifying some of the problems of glomerular pathology, and also serve as the necessary intermediate step to electron microscopy.

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NORMAL KIDNEY

The main features of glomerular architecture are well established. They may be represented as follows: The afferent arteriole dilates after entering the glomerulus to form the infundibulum. Arising from the latter are several short trunks each supplying directly, or after subdivision, a lobe of the glomerulus. These lobar trunks do not anastomose. Each lobe is drained by a tributary of the efferent arteriole. Between the afferent and the efferent trunks are interposed branching and twisting lobular capillaries which form glomerular lobules. In addition, the afferent and the efferent beds within the lobe may be connected by short direct anastomoses bypassing the lobules.

The vessels of the glomerular root, i.e., the afferent arteriole and infundibulum and the efferent arteriole, are invested on all sides by a thin mantle of connective tissue fibers and cells. The mantle extends along the major, lobar branches, afferent as well as efferent, gradually becoming attenuated towards the periphery. The lobular capillaries do not have a connective tissue covering. However, each capillary winds around the central core of the lobule, composed of cells and fibers lying in the so-called intercapillary space. The existence of this space is still disputed by some students of renal anatomy (10), but there is good evidence in its favor derived from study of normal and abnormal histology by means of light, phase and electron microscopy. Elias (11) has shown by mathematical calculation that part of the space enclosed by the basement membrane must be solid rather than hollow, otherwise the total volume of the capillaries would far exceed the size of the entire glomerulus. Glomerular capillaries do not float freely in Bowman's space, merely suspended at the glomerular root, but are held together by the cells and fibers in the intercapillary space.

The nature of these intercapillary cells and fibers has not been definitely established. Most observers, beginning with Zimmermann (12) believe them to be of mesenchymal origin, and the intercapillary space to be continuous with the connective tissue mantle of the glomerular root. The term mesangium is used to designate the entire connective tissue system of the glomerulus. Yamada (13) suggested that the cells of the intercapillary space are myoid in nature, while the fibers represent ramifications of the basement membrane. Other electron microscopists (14, 15) proposed that the space is filled by a solid core of endothelial cells whose cytoplasmic extensions form the actual inner lining of the capillaries. Elias (11) offered the name endenchyma to designate this cellular core.

The intercapillary structures are inconspicuous in the normal glomerulus, though they can be readily demonstrated in thin sections (Fig. 1). The importance of the space lies in the fact that it is a frequent seat of disease processes affecting the glomerulus, be it of inflammatory (glomerulonephritis) or degenerative (arteriosclerosis, diabetes, amyloidosis) nature.

The structure of the wall of the glomerular capillaries has been recently clarified by electron microscopy (13, 14, 16). The epithelial cells do not rest directly on the capillary basement membrane but are supported by narrow trabeculae

and interdigitating foot processes. The basement membrane proper (lamina densa of Hall) consists of three layers: the dense middle zone, and narrower inner and outer zones of lower electron densities. The capillary lumen is lined by very thin endothelial cytoplasm showing fine perforations (lamina fenestrata or attenuata of Hall). The capillary wall participates in a variety of disease processes, though not necessarily in the same manner as the intercapillary space.

ABNORMAL KIDNEY

The thin section technique has been applied to various types of glomerular lesions, both inflammatory and degenerative. The findings in glomerulonephritis and in intercapillary glomerulosclerosis may serve as illustrative examples of the results obtained.

Acute Glomerulonephritis

The question of the nature and localization of the inflammatory process in the glomerulus has been re-opened by Jones (2). Acute glomerulonephritis is characterized by the appearance of large numbers of mononuclear cells and, later, fibers in the glomerulus. These have been at first conceived as of connective tissue origin, later as epithelial, and currently as endothelial. The historical development of these concepts has been traced elsewhere (8). In his recent papers (2, 17) Jones presented evidence that inflammation takes place in the inter-

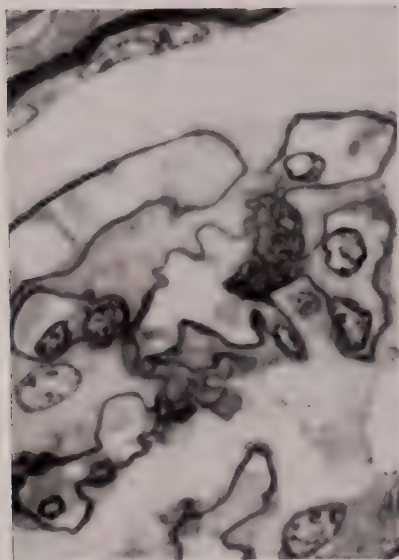


FIG. 1

FIG. 1. Normal glomerular lobule. Capillaries are separated by intercapillary spaces (dark) containing fibers and cells. Note prominent endothelial nuclei and pale staining red cells in the capillary lumina. Thin section, PAS, $\times 1700$.

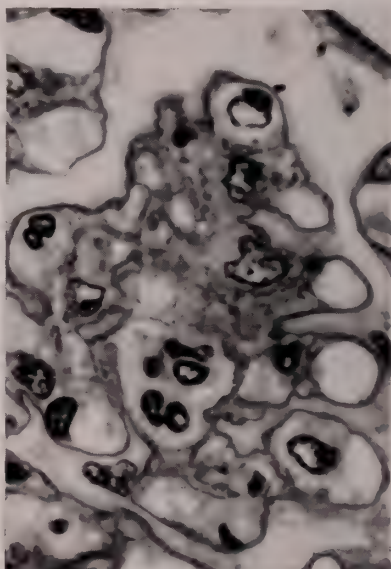


FIG. 2

FIG. 2. Glomerular lobule in early acute glomerulonephritis. The intercapillary space is distended by edema. Capillaries contain polymorphonuclear leukocytes. Thin section, PAS, $\times 1700$.

capillary space and again suggested that the cells and fibers are of connective tissue or histiocytic origin. There is much in support of this claim, but the question cannot be settled until the nature of intercapillary cells and fibers in the normal glomerulus, and their relation to those observed in disease, is definitely determined. There is little doubt, however, that inflammation affects mainly the intercapillary space. The evolution of this process can be clearly traced in half micron sections (8, 18). In the earliest stage of acute glomerulonephritis, accumulation of polymorphonuclear leukocytes and swelling, and perhaps limited proliferation of endothelial cells, is seen in the capillary lumina. This stage is rapidly followed by exudation of leukocytes and fluid into the intercapillary space and enlargement of the lobular centers (Fig. 2). Further distension of the intercapillary space by proliferating mononuclear cells leads to compression of the capillaries against the basement membrane and consequent ischemia. Sometimes the capillary is detached from the basement membrane by accumulation of fluid and cells. At the height of the disease, the lobule is no more than a "balloon" filled with fluid and inflammatory cells. As the inflammation recedes, the lobular centers decrease in size and the capillaries that have not been permanently damaged, reopen. If complete resolution does not follow, the continued activity of the process is attested to by the appearance of fibers in the intercapillary space. At first these are thin and sparse, but soon become thick and tortuous. In their staining reactions, though not in appearance, these fibers resemble the normal

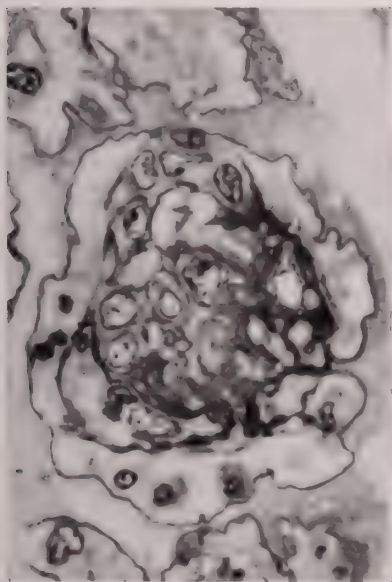


FIG. 3

FIG. 3. Glomerular lobule in subacute glomerulonephritis. The intercapillary space is filled with mononuclear cells and fibers. The capillary circles the periphery of the lobule. Thin section, PAS, $\times 1400$.

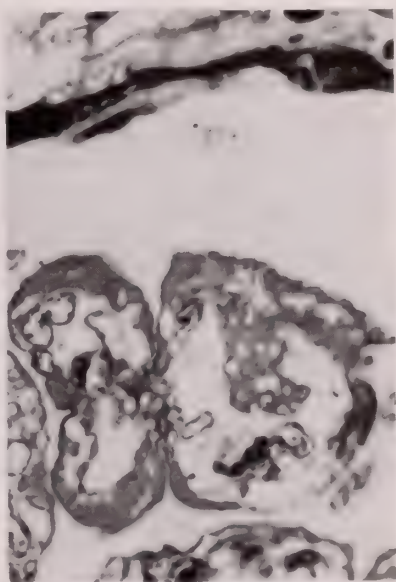


FIG. 4

FIG. 4. Subacute glomerulonephritis. Deposits of hyalin on the inside of the capillary basement membrane, simulating "wire loops". Thin section, PAS, $\times 1700$.

fibers of the connective tissue surrounding the glomerular root. They have been observed as early as the twelfth day of illness. Their presence signals transition from the acute to the subacute stage of glomerulonephritis.

Subacute Glomerulonephritis

While acute diffuse glomerulonephritis follows the same mode of development in every instance, differing only in degree, the subacute stage presents various combinations of intercapillary inflammation and fibrosis, deposition of hyalin, alteration of the capillary wall and proliferation of epithelial cells, so as to impart almost an individual pattern to each case.

The intercapillary changes are the direct result of unresolved acute disease. The enlarged lobular centers are filled with fibers, mononuclear cells and a few leukocytes, and are surrounded by a peripheral wreath of capillaries (Fig. 3). The fibers stain blue with trichrome stain (chromotrope-aniline blue) and red with periodic acid-Schiff's reagent (PAS). Accumulation of fibers and cells is also seen around the vessels of the glomerular hilus. As the disease progresses towards the chronic stage, the number of fibers increases at the expense of cells and the capillaries gradually collapse.

Deposition of hyalin is a frequent but not an invariable feature of subacute glomerulonephritis. The hyalin is found in the fibrosed lobular centers, in the capillary walls and capillary lumina, in the epithelial cells and in the arterioles. It stains red with PAS reagent and usually red with chromotrope-aniline blue.

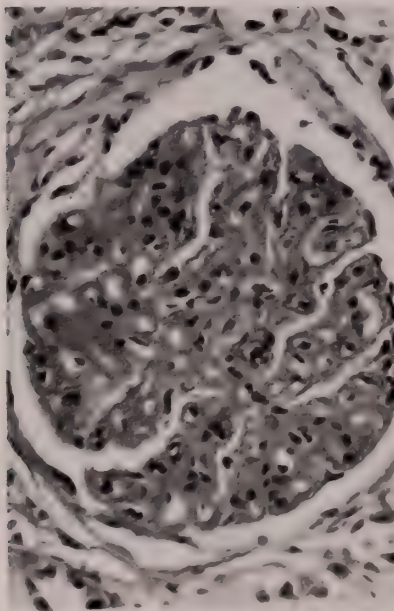


FIG. 5. A.

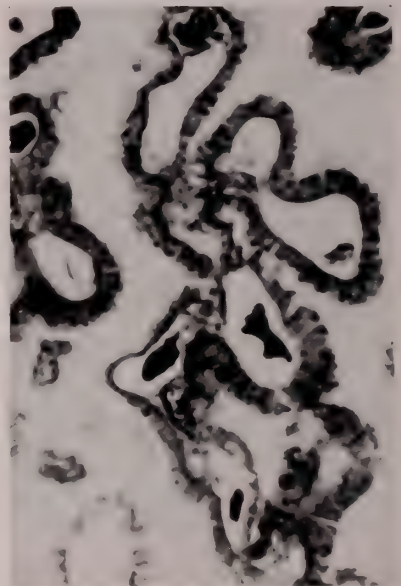


FIG. 5. B.

FIG. 5. A. Membranous transformation ("membranous glomerulonephritis"). The capillary walls are very thick. The lumina are narrow. Standard section, Hematoxylin and Eosin, $\times 350$. B. Detailed structure of the capillary walls. Periodic alternation of light and dark (red and blue) bands. Thin section, Chromotrope-Aniline blue, $\times 1700$.

Alteration of the capillary wall that is most frequently seen is reduplication or splitting of the basement membrane into two layers, the outer layer being thicker and often wrinkled, the inner, very thin and delicate. If hyalin is deposited between the split layers, or on the inside of the basement membrane, the whole wall assumes the appearance of a thick membrane (membranous transformation). This transformation is focal and variable; when sufficiently advanced, it gives rise to lesions closely resembling the "wire loops" of disseminated lupus erythematosus (Fig. 4). The hyalin is homogeneous or slightly vacuolated, red with periodic acid-Schiff's reagent and intensely red with chromotrope-aniline blue.

Another type of membranous transformation ("membranous glomerulonephritis") has been associated by Bell (1) with lipoid nephrosis or nephrotic phase of subacute glomerulonephritis (Fig. 5A). This lesion is diffuse and uniform, involving most of the glomeruli. It is characterized by formation of a broad zone between the basement membrane and the epithelial cells. This zone has typical periodic structure (Fig. 5B) and consists of bands, perpendicular to the basement membrane, alternately PAS positive and negative, or respectively, blue and red with chromotrope-aniline blue. The periodicity is on the order of 0.5–0.7 micron; it may be in some way related to the trabeculae and foot processes of the epithelial cells.

The epithelial crescents arise by proliferation of the cells lining the Bowman's capsule. The crescents are frequently interlaced with thin fibers, or perhaps membranes, which arise from the basement membrane of the Bowman's capsule and contribute to formation of pseudo-tubules. These fibers are at first PAS

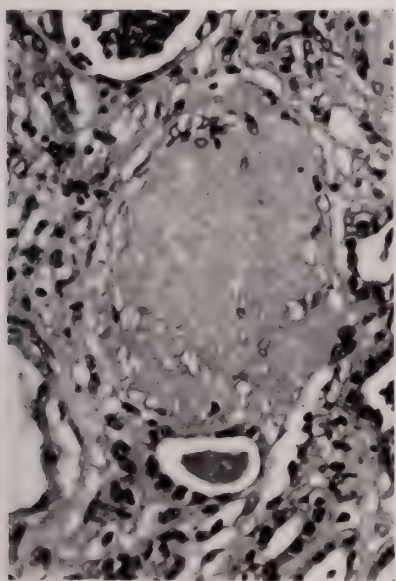


FIG. 6. A.

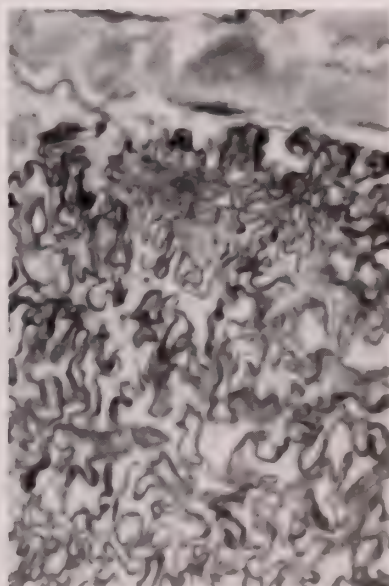


FIG. 6. B.

Fig. 6. A. Collapsed ("fibrosed") glomerulus in chronic glomerulonephritis. Standard section, Hematoxylin and Eosin, $\times 350$. B. Total collapse of capillaries and disappearance of cells. Thin section, PAS, $\times 1700$.

positive; later they become thicker and PAS negative, while retaining their affinity for aniline blue. Fibrous crescents derive either from cellular crescents, or directly from the basement membrane of Bowman's capsule, through splitting, reduplication and fibrosis.

Chronic Glomerulonephritis

The obsolete glomerulus of chronic glomerulonephritis (and likewise, the glomerulus of vascular renal disease) is usually referred to as fibrosed or hyalinized. Study of glomerular obsolescence suggests that these three terms are not necessarily synonymous. The essential feature of obsolescence is collapse of the capillaries. This can be brought about by fibrosis within the glomerulus or by a combination of fibrosis and hyalinization. It can be demonstrated by means of thin sections, that in a number of instances an obsolete glomerulus is neither fibrosed nor hyalinized, but merely collapsed, and consists of nothing more than a tangle of basement membranes (Figs. 6A and B). These basement membranes may be changed by the disease process, split or wrinkled, or accompanied by membranous transformation; on occasion they appear entirely unaltered. The lumina of the incompletely collapsed capillaries may be filled with homogeneous eosinophilic material which stains pale pink with PAS and probably represents inspissated plasma proteins.

Diabetic Glomerulosclerosis

Sclerosis and obsolescence of glomeruli in diabetes is caused by deposition of fibers and hyalin. These same factors are the cause of glomerular obsolescence

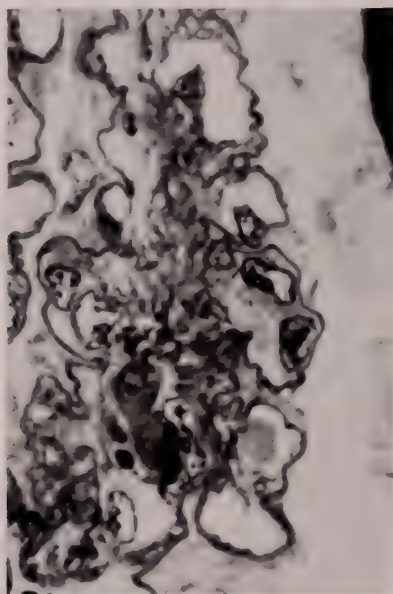


FIG. 7. Intercapillary (diabetic) glomerulosclerosis. Fibers and early hyalin deposit in the intercapillary space. Note structural resemblance to Fig. 2. Thin section, PAS, $\times 1700$.

in most instances of glomerulonephritis. The difference between the two diseases lies in localization and structure of the fibers and the hyalin. Normal aging of the glomerulus is accompanied by an increase in the number of fibers around the hilus and in the intercapillary space. This increase is accentuated by arteriosclerosis. In diabetic sclerosis the fibers are even more numerous. They are roughly uniform in thickness, straight or wavy, but not gnarled and twisted as in glomerulonephritis. They extend in parallel bundles along the major lobar capillaries and their branches, from the hilus to the lobular centers, and are primarily responsible for what Bell named the diffuse type of intercapillary sclerosis.

The typical nodular lesions of diabetic glomerulosclerosis are produced when hyalin and fibers are deposited in the lobular centers (Fig. 7). The proportion of fibers and hyalin varies, but it is the combination of the two that imparts to the nodules their typical appearance. Sometimes hyalin extends in the direction of the hilus, surrounding the major lobar trunks. Because of similarity in staining, particularly with eosin and with PAS, fibers and hyalin may be difficult to tell apart except by means of thin sections, and by means of some of the special stains, such as chromotrope-aniline blue or silver.

Not infrequently, the capillary adjoining a hyalin nodule is straightened and dilated (capillary aneurysm of Allen). It may be filled with vacuolated acidophilic material, possibly inspissated plasma proteins rich in lipoids and perhaps also in abnormal proteins. In the later stages of the disease, the capillaries become compressed by expansion of the nodules. The obsolete, hyalinized glomerulus of diabetes is often larger than a normal glomerulus (hypertrophic obsolescence), while the glomerulus of chronic glomerulonephritis is smaller than normal (atrophic obsolescence).

CONCLUSIONS

Stained thin (one half micron) sections are useful in the study of anatomy and pathology of the kidney. It is suggested that such sections may be of value in examination of various organs and tissues as a method per se, and as an intermediate step to electron microscopy.

The renal glomerulus is a particularly instructive field of study because it reflects and amplifies the behavior of the filtration segment of the body capillaries.

Inflammation and degeneration of the glomerulus involves primarily the central cores of the lobules (intercapillary space). The walls of the capillaries show various types of alteration, either focal or diffuse (membranous transformation).

Deposition of hyalin is an important factor in glomerular pathology of inflammatory or degenerative origin. This again raises the question of disturbance in protein metabolism (paraproteinosis), particularly in subacute glomerulonephritis and in diabetes.

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A STUDY OF CONGENITAL HEART DISEASE SEEN AT NECROPSY IN A LARGE GENERAL HOSPITAL IN HAWAII

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From January 1, 1944 through December 31, 1956, 46 cases of congenital cardiac disease were recorded in the necropsy files of the Queen's Hospital, Honolulu, T. H., constituting about one per cent of the pool from which they were collected. This percentage is not suggested as indicating the incidence of malformations of the heart in the Territory of Hawaii. The purpose of this paper rather is to point up the status of this affliction in a large general hospital in the Hawaiian Islands.

The distribution of cases in this series along with ages, sexes, and races is listed in Table I.

The listings in the table are of the major defects; often lesser defects were present also. The racial classification is one in common use in the Territory of Hawaii and accepted by its Board of Health although deviation from anthropological nosology is recognized. Where the number of "races" listed is less than the number of cases, either some races were represented by several examples or racial extraction could not be determined. Where more races than cases are listed, this is due to the fact that ethnic combinations occurred.

Of the patients with the commonest major defect in this series, only the 55 year old lived more than 41 days. His heart showed a communication between the left ventricle and the right atrium and weighed 836 grams, the largest in this series. A congenitally bicuspid aortic valve was present. The patient died of a micrococcus pyogenes (var. albus) endocarditis involving the aortic valve and the rim of the septal defect. One stillborn weighing one pound and eight ounces also showed a communication between the left ventricular and right atrial cardiac chambers. In all other cases communications were between ventricular chambers. An astonishing feature of this group was the occurrence of the defect in the muscular septum in four males. Two of these showed pulmonary pictures resembling congenital alveolar dysplasia of Mac Mahon (1) and all four had hemorrhages although in different sites.

The stenoses in the tetralogy of Fallot were infundibular twice, valvular twice, and combined valvular and infundibular once. All patients with this anomaly were polycythemic and all except the youngest had recognizable murmurs and clubbing of fingers and toes. Where histories were adequate and x-ray readings were available cyanosis had always been present at birth and the clinical and x-ray features had suggested the diagnosis. At necropsy degenerative verrucal endocardioses (2) of the pulmonic valve and of the right ventricular outflow tract were each seen once. Microscopic examination of lungs of two patients revealed thickening of the walls of the intrapulmonary vessels. This was

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TABLE I

Defect	No. Cases	Sex		Age Range	Races
		Male	Female		
Ventricular septal defect	10	9	1	Premature still-born to 55 years	Japanese, Chinese, Caucasian
Tetralogy of Fallot (Ventricular septal defect, right heart hypertrophy, biventricular take-off of the aorta, and pulmonic area stenosis)	5	3	2	15 months to 23 years	Filipino, Chinese, Japanese, Hawaiian, Caucasian
Complete transposition of the aorta	6	4	2	34 hours to 14 months	Hawaiian, Portuguese, Chinese, Japanese, Caucasian
Persistent common atrioventricular canal	4	2	2	Stillborn term to 5 years	Japanese, Filipino, Caucasian
Ebstein's malformation of the tricuspid valve (downward displacement of septal and posterior leaflets of the tricuspid valve and tricuspid insufficiency)	2	1	1	23 years to 36 years	Hawaiian, Caucasian, Japanese
Coarctation of the aorta	2	1	1	6 months premature to 35 years	Filipino, Japanese
Cor biloculare	2	1	1	1 day-2 days	Japanese
Endocardial fibroelastosis	4	2	2	3 months-1½ years	Hawaiian, Filipino
Atrial septal defect	3	3	0	59 years-89 years	Hawaiian
Pulmonary valve atresia or stenosis	2	1	1	6 days and 21 years	Japanese
Eisenmenger's Complex (Ventricular septal defect, right heart hypertrophy, biventricular take-off of aorta, and no pulmonic area stenosis)	3	1	2	2 days to 32 years	Japanese
Anomalous drainage of pulmonary veins	1	1	0	2½ months	Hawaiian
Patent ductus arteriosus	1	1	0	19 years	Filipino
Persistent truncus arteriosus	1	1	0	3 days	Japanese

associated with intimal thickening in chronic pneumonitis in one case and with medial hypertrophy in chronic emphysema in the second. A persistent left superior vena cava which emptied into the coronary sinus was found in one case. There were two postoperative deaths: one due to cardiac failure after an end to end anastomosis of the right pulmonary and subclavian arteries; and the second due to cerebral thrombosis following an anastomosis between the main trunk of the pulmonary artery and the aorta. Operation was withheld on a 2½ year old

child who died of multiple cerebral abscesses. The other two patients of this group died in cardiac decompensation.

A distinctive feature of the cases with complete transposition of the great vessels was the occurrence in three patients of part Hawaiian ancestry. This particular finding is noted since Hawaiians are in the minority in the Islands and neither this particular distribution nor any trend concerning any race was found in any other anomaly in this series. A patent foramen ovale was found in every heart but one in the transpositions as would be expected in the ages in this group. One heart had an associated ventricular septal defect and the patient had an unusual and unfortunate demise brought about by a myxoma of the tricuspid valve which pushed through and plugged the defect with subsequent cardiac failure. An excessively patent ductus was present in another case, 15 days old, in this series. One patient had only a small 5 mm. band of muscle (crista supraventricularis) separating the pulmonary artery from the ventricular septal defect. This was close to a so-called Taussig-Bing heart since the pulmonary artery was larger than the aorta and except for the above mentioned band would have overridden both ventricles.

Persistent common atrioventricular canal was always of the complete type (3) and was associated with Mongolism three times and with hydrocephaly, anophthalmia, incomplete rotation of the intestine, bilobed right lung, polydactylism, and adrenal agenesis once. The oldest case died in failure and the others were either stillborn or lived only a short period. No patient with a clinical diagnosis of Mongolism who came to necropsy failed to show a persistent common atrioventricular canal. One Mongoloid with a common canal also showed a persistent truncus arteriosus with the pulmonary arteries coming off from it. This was listed as a persistent truncus because that was the most important anomaly and the patient had the most pronounced cyanosis of any case in this series. At necropsy absence of the gall bladder was noted, grossly, as was congenital alveolar dysplasia of the lungs, microscopically.

Ebstein's malformation of the tricuspid valve results in the inclusion of an appreciable amount of right ventricular musculature into the right atrium resulting in great enlargement of the latter chamber. One of the patients with this malformation has been reported elsewhere (4). He had a patent foramen ovale and a Wolff-Parkinson-White arrhythmia, and he died of a micrococcus pyogenes (var. aureus) cerebral abscess. The second case entered the hospital with evidence of cardiac failure and was twice operated upon: once because of an x-ray picture suggestive of tumor; and the second time because of disagreement in diagnosis, some still diagnosing tumor, and others favoring Ebstein's. The patient died of cardiac failure and pericarditis postoperatively. The clinicians involved in these cases are convinced of the importance of considering Ebstein's malformation in the differential diagnosis of enlarged right auricle without evidence of rheumatic heart disease. Furthermore, the importance of operative treatment for patent foramen ovale where present is suggested by the cerebral abscess.

Two of the atrial septal defects were of the banal patent foramen ovale type

and the other was a true large atrial septal defect involving more than the foramen ovale alone and measuring 4 cm. in diameter. This latter occurred in a patient who died of pulmonary embolism from an undetermined source. He had been diagnosed clinically as congenital heart disease, but the type had been undetermined pre-mortem.

One of the three Eisenmenger cases was a stevedore who died at the age of 32 when crushed by a crane. He was known to have a murmur and had been diagnosed as having congenital heart disease, but had been entirely asymptomatic. Another patient, 2 days of age, had an associated congenital cataract of the left eye, a hemangioma of the scalp, and a flexion deformity of both index fingers. This child was cyanotic from birth. All her five siblings were normal.

All cases of endocardial sclerosis or fibroelastosis were of the dilated type of Edwards (5). The hearts were all hypertrophied and globular. One case showed minimal fibroelastosis and if this is not accepted as the etiology of the enlargement, it can only be classified by us as the "idiopathic hypertrophy" of Stoloff (6). Two of these cases were suspected of having some undetermined type of congenital cardiac disease clinically. In all cases death was relatively sudden.

Both bilocular hearts had large atrial septal defects, common atrioventricular canals, single ventricles, and rudimentary atrial and ventricular septa. One heart showed, in addition, atresia of the aortic valve with hypoplasia of the aorta. A rudimentary outflow tract, transposition of the great vessels, and origin of the aorta from the rudimentary chamber were present in the other.

No case of coarctation of the aorta has come to operation in the territory, as near as can be told. In this series the infant had a short narrow segment proximal to the aortic insertion of the ductus arteriosus. The aortic luminal diameter changed from 8 mm. to 3 mm. in the narrow segment. The pulmonic mouth of the ductus was patent but the aortic end was closed by a diaphragm like formation. The lower two-thirds of the body was poorly developed. The adult patient had a long history of hypertension and occipital headaches. The blood pressure was higher in the right than in the left arm. Death was due to intracranial hemorrhage. At necropsy there was a cleft like narrowing of the aorta with a corresponding ridge like thickening intraluminally between the origins of the left common carotid and left subclavian arteries. Beyond this narrowing the entire aorta was hypoplastic. Atherosclerosis was present proximal to the coarctation and absent distal to it.

One of the patients with pulmonic valvular abnormality, a Japanese female who survived six days, had an atresia. There was, in addition, evidence of endocardial sclerosis (fibroelastosis) of the dilated type involving the left ventricle. Most unusual were nodular areas of sclerosis of the coronary arteries, especially the right. Microscopically the sclerosis was intimal. This is not necessarily evidence of anoxia causing fibroelastosis, since the major coronary disease and the endocardial changes tended to be on opposite sides of the heart. The second case died of acute lymphocytic leukemia. A stenotic pulmonic valve showed fusion of cusps, one of which was bifid. The valvular circumference at the annulus fibrosus was 5 cm., but at the orifice it was less than 0.7 cm. The heart weighed 410

grams due chiefly to hypertrophy of the right ventricle. A patent foramen ovale was also present. Clinically the patient was found to have a loud systolic murmur in the pulmonary area during his induction physical, and he was rejected with a diagnosis of congenital heart disease. Cyanosis was not recorded and it may be that gradual dilation of the right ventricle converted a probe patent foramen into a functional and anatomical one. By this time cyanosis might not have been apparent because of the anemia resulting from the leukemic state.

Single cases of anomalous drainage of pulmonary veins into the right auricle and of patent ductus were also seen. The former anomaly had associated right ventricular infundibular hypertrophy and a patent foramen ovale. Cyanosis, absent at birth, developed about the age of six weeks. The patent ductus was of the window type. The patient died of acute hepatitis. There was no record of previous physicals but the patient on admission had clubbing of fingers and toes, and he was cyanotic terminally. No murmurs were recorded. The ductal (aortic-pulmonic window) diameter was 2 cm. Of interest is the fact that more than 15 cases of patent ductus have been successfully operated upon in the territory during the last half of the period covered by this study.

SUMMARY

A review of cases of congenital heart disease autopsied in a large general hospital in the Territory of Hawaii revealed findings not significantly different from those described from other areas. Ventricular septal defects and complete transposition of the great vessels constituted over $1\frac{1}{3}$ of the cases in this study. A large percentage (40 per cent) of the former showed defects in the muscular septum. Both ventricular septal defect and complete transposition occurred predominantly in males, and the latter showed an unusual tendency toward occurrence in individuals of part Hawaiian ancestry. The point is emphasized that the findings here are not of statistical significance. Rare cases included two of Ebstein's malformation of the tricuspid valve and one of an infant with intimal sclerosis in the coronary arteries. The incidence of congenital cardiac disease was about one per cent of the pool from which these cases were drawn.

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TUMOR-LIKE PROLIFERATIONS OF LYMPHOID TISSUE

OCCURRENCE IN DELTOID MUSCLE AND MEDIASTINUM

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INTRODUCTION

Conspicuous proliferation of lymphoid tissue resulting from chronic inflammation or reactive hyperplasia is common in organs and tissues where lymphoid tissue may or may not normally reside. A few familiar examples are tonsillar and nontonsillar tissues of the pharynx, thyroid gland in hyperthyroidism and Hashimoto's disease, submaxillary salivary gland in sialolithiasis, branchial cleft cyst, intestine in regional enteritis, cervix uteri, urinary bladder, prostate gland, etc. The lymphoid tissue growth under such and other reactive states may be pronounced, yet an actual mass or tumor-like formation of the lymphoid tissue usually does not occur. One exception is the lymphoid polyp of the rectum, considered by some to be hyperplastic lymphoid tissue (1). Even in lymph nodes, though enlargement may be marked in inflammations and hyperplasias, large growths rarely develop unless a neoplasm is present. However, recently Castleman, Iverson, and Menendez reported a series of mediastinal growths resulting from localized hyperplasia in lymph nodes (2). The present report concerns itself with a study of two cases in which there was a sizable mass of lymphoid tissue of unusual structure and in unusual locations, one in the substance of the deltoid muscle, the other in the mediastinum.

CASE REPORTS

Case I. D. A. N., female age 14 years, admitted to Menorah Medical Center on 10-20-53 for removal of a growth in the deltoid region of the left arm, present for $2\frac{1}{2}$ years. The growth first appeared as a small nodule, slightly painful and tender; it has gradually increased in size and there is no longer pain. The parents believe the nodule developed at the site of an immunization injection which the child received shortly before the lesion was first noted. The records of the county health office verified that the child received a booster injection intramuscularly of 1 cc. of diphtheria-tetanus alum precipitated toxoid on 3-27-51. Examination revealed a deep, freely-movable firm mass measuring 5 x 3 cm. not tender and not fixed to bone or skin. Liver, spleen, cervical and axillary lymph nodes were not palpable; inguinal lymph nodes bilaterally were slightly enlarged. X-ray examinations of the left humerus and chest were negative, as were routine blood count, urinalysis and serological examination of blood. On 10-21-53 the lesion was surgically removed with a wide margin of normal surrounding muscle. It lay in the substance of the deltoid muscle, being completely surrounded on all sides by muscle. There have been regular follow-up examinations at intervals of 6 months. The patient is well and there is no sign of local recurrence through December, 1956, 3 years after operation.

Pathology-Gross (Fig. 1). Rubbery ovoid mass measuring 5.5 x 4 x 3 cm., weighing 33 gm. External surface smooth, generally encapsulated. Sectioned surface slightly bulging, pale, tannish brown, homogeneous except for fine white trabeculations. Moderate amount of skeletal muscle is attached. The muscle

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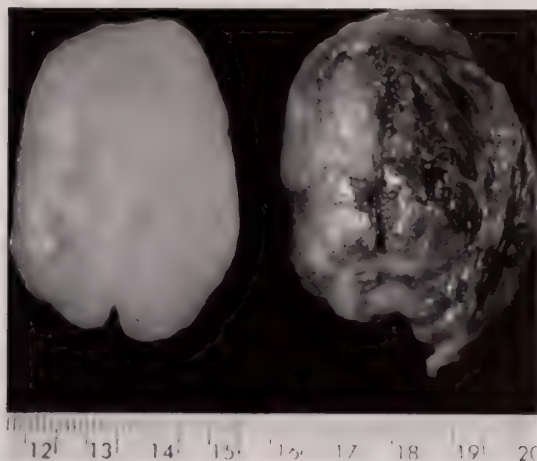


FIG. 1. Case I—Gross specimen. Cut surface, left. Muscle attached to external surface, right.

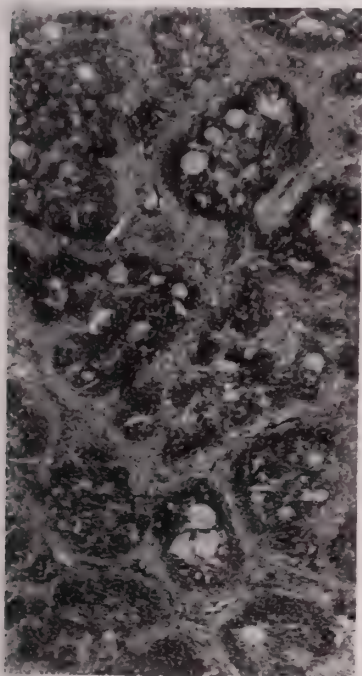


FIG. 2

FIG. 2. Case I—Low power showing large nodules of lymphoid tissue with multiple reaction centers. Internodular bands of less cellular tissue, $\times 20$.

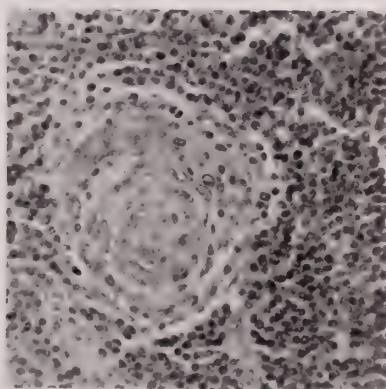


FIG. 3

FIG. 3. Case I—Whorled reaction center in a lymphoid follicle, $\times 210$.

generally is loosely adherent except in one place; here it is fixed and there is suspicious extension of tissue from the mass into the muscle. Received separately skeletal muscle measuring $6.5 \times 4 \times 1$ cm. and free of significant changes.

Microscopic. A well defined hyalinized fibrous capsule surrounds the major

part of the lesion. Only one of a number of sections shows a small deficiency in the capsule where lymphoid tissue of the mass is in direct contact with, but sharply demarcated from, surrounding muscle without actually penetrating it. The immediately surrounding muscle has large blood vessels, increased fibrous tissue and occasional tiny foci of small lymphocytes in the interstitial septa; muscle farther removed is free of changes. Stout hyalinized fibrous trabeculae,

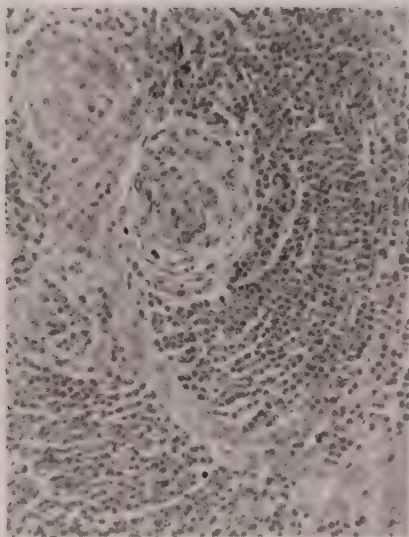


FIG. 4

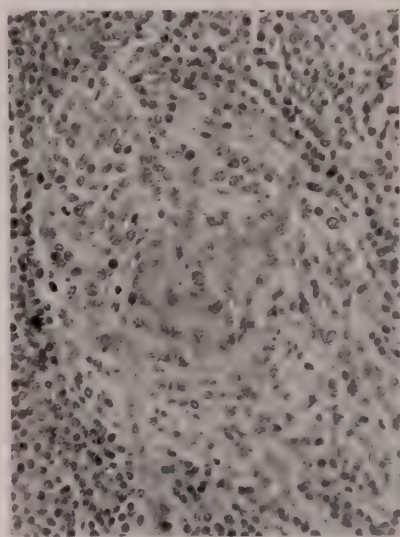


FIG. 5

FIG. 4. Case I—Follicle with a penetrating capillary skirting reaction center and terminating in a ball of proliferated endothelial cells, above and to left of reaction center. Origin of capillary from parent vessel in internodular tissue below and to right, $\times 210$.

FIG. 5. Case I—Reaction center invaded by capillaries from several directions and transforming its central portion, $\times 210$.

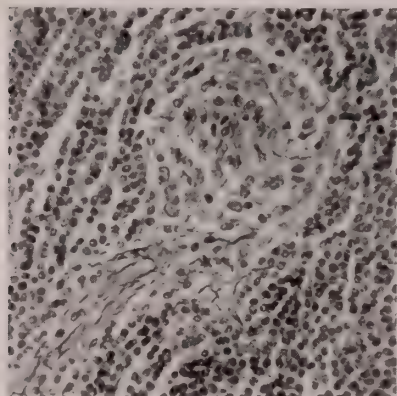


FIG. 6

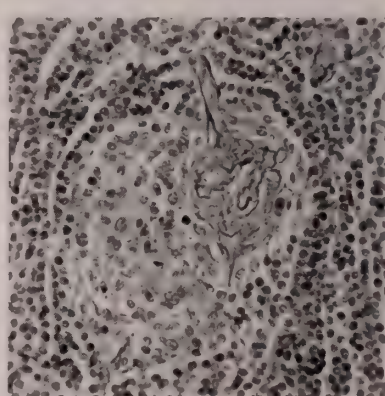


FIG. 7

FIG. 6. Case I—Nodule penetrated by capillary extending to, but not invading, reaction center. Reticulum stain, $\times 210$.

FIG. 7. Case I—Reaction center invaded by capillary and showing tangled net of reticulum fibers in right part of center, left part unaffected. Reticulum stain, $\times 210$.

continuous with the capsule, course through the lesion. The mass is composed of large nodules or lobules of compact lymphoid tissue separated by bands of less cellular lymphoid tissue (Fig. 2). The nodules are larger than the follicles of a normal or hyperplastic lymph node and range from 0.34 to 1.7 mm. in diameter. Peripherally in the nodules are small lymphocytes and centrally are one or more well defined nests of larger and looser cells characteristically whorled and con-

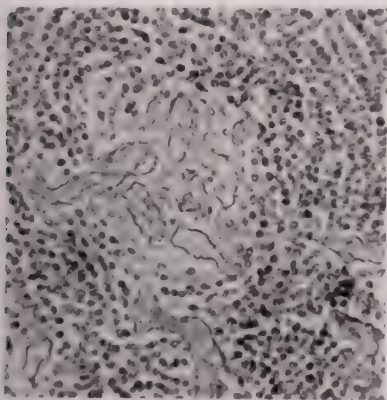


FIG. 8

FIG. 8. Case I—Reaction center extensively transformed by reticulum derived from invading capillaries. Reticulum stain, $\times 210$.

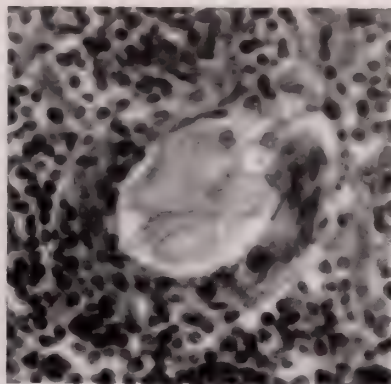


FIG. 9

FIG. 9. Case I—Crystals in center of follicle. Larger cells concentrically around crystals. Frozen section, $\times 400$.

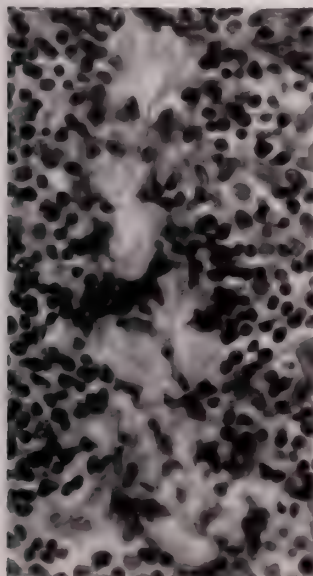


FIG. 10



FIG. 11

FIG. 10. Case I—Crystals in interfollicular cord. Frozen section, $\times 400$.

FIG. 11. Case I—Same as Fig. 10. Photograph taken through crossed polarizing filters to show that crystals are doubly refractile.

stituting the reaction centers (Fig. 3). Not infrequently the centers bear a resemblance to epithelioid cell granulomas. A striking feature of the lesion is the penetration of the lymphoid nodules by capillaries from the internodular stroma. These occur as 1 or more ingrowing sprouts or fascicles that invade the nodules from different directions and may produce pronounced distortion and disruption of the nodules. The reaction centers may be spared or extensively involved (Figs. 4-8). The capillaries have large hyperplastic endothelial cells and abundant reticulum fibers, which when intermixed with the reaction center cells result in a transformed center where it becomes almost impossible to recognize which cells

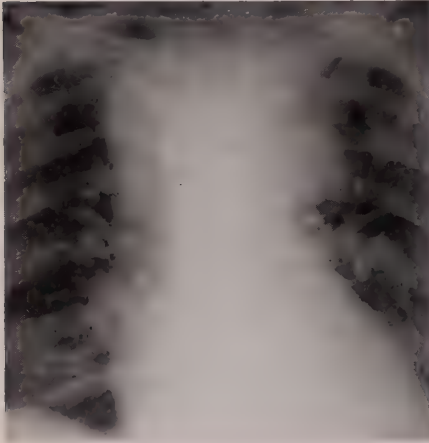


FIG. 12

FIG. 12. Case II—X-ray of chest, A. P. Mass in superior mediastinum. Esophagus and trachea displaced to right.

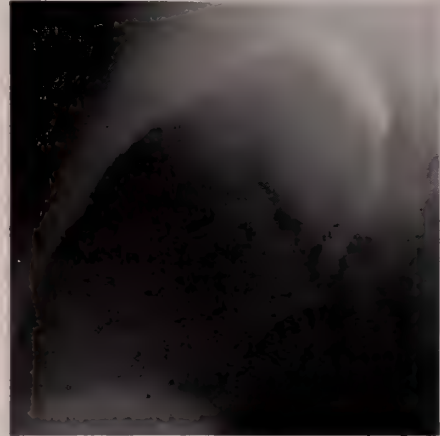


FIG. 13

FIG. 13. Case II—X-ray of chest, lateral. Mass lying between posteriorly displaced esophagus and anteriorly displaced trachea.

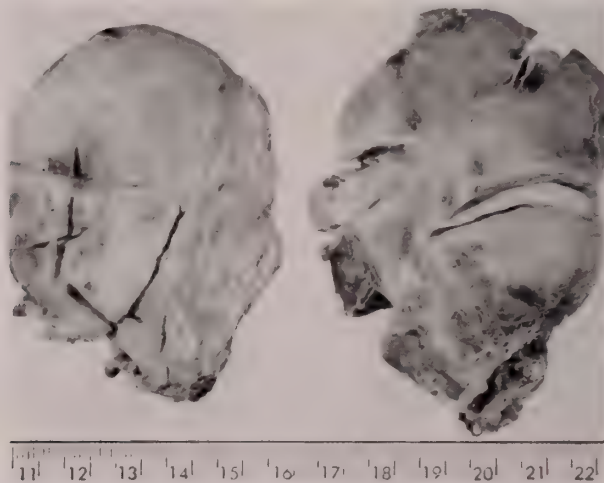


FIG. 14. Case II—Gross specimen. Cut surface, left. External surface, right.

are endothelial and which are reaction center cells. The internodular tissue forms broad bands of small lymphocytes and capillaries which are abundant, lumens are compressed and inconspicuous, and the endothelial cells are hyperplastic and have plump nuclei. Here reticulum fibers are abundant and are derived chiefly from the proliferated capillaries. Hyalinized fibers derived from capillary walls may be prominent both in the internodular cords and lymphoid follicles. There are a few plasma cells. Peripheral and/or central sinuses, as occur in lymph nodes, cannot be found. In the routinely stained hematoxylin and eosin sections there are diffusely a number of well defined, clear, empty spaces with irregular margins. They occupy the interfollicular cords, peripheries and centers of follicles, and even the

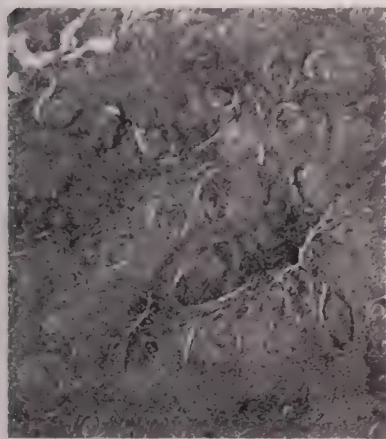


FIG. 15

FIG. 15. Case II—Low power showing lymphoid follicles and abundant interfollicular tissue, $\times 20$.

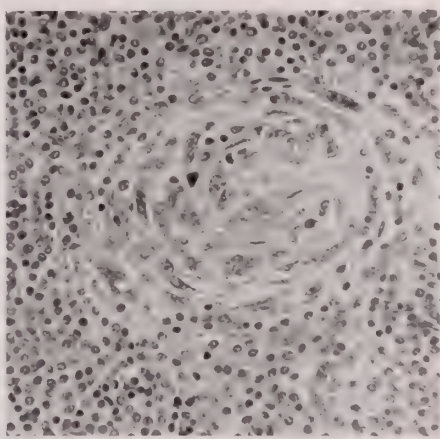


FIG. 16

FIG. 16. Case II—Follicle with whorled reaction center, $\times 210$.

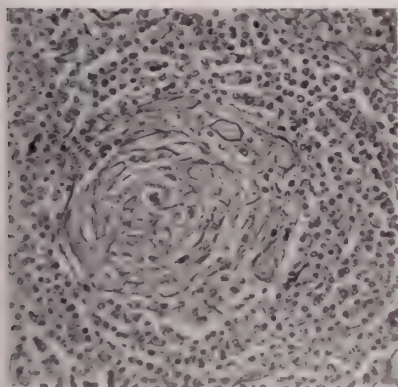


FIG. 17

FIG. 17. Case II—Follicle whose reaction center is converted into a tangled nest of reticulum fibers and cells. Reticulum stain, $\times 160$.

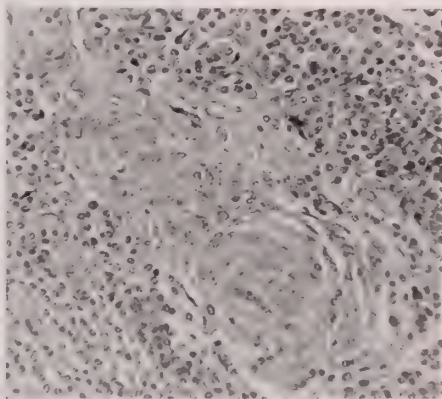


FIG. 18

FIG. 18. Case II—Follicle penetrated and transformed by capillary endothelial cells, $\times 160$.

fibrous trabeculae. In frozen sections of formalin fixed tissue there are numerous aggregates of crystals which correspond precisely in distribution, size, and shape to the spaces (Figs. 9-11). The crystals are colorless, pointed or needle shaped, doubly refractile and occur in sheaves, fern-like, and rounded bodies where they commonly assume a radiating pattern. In the centers of follicles they may be surrounded by concentric layers of large cells, as if the latter were attempting to engulf the crystals (Fig. 9). Aside from this the crystals appear not to have provoked any special type of cellular response, and no histiocytes, giant cells, or fibrous tissue are noted in the vicinity of the crystals. The crystals do not stain with Oil Red O.

Case II. E. A., female age 58 years, admitted to St. Joseph Hospital, Kansas City, Mo. on 7-26-54. During the preceding 6 months there have been pain and discomfort in the chest aggravated by exertion, palpitation and dyspnea on exertion, weakness, and cough without expectoration, all symptoms increasing in severity. Examination revealed coarse respiratory wheezes in both lungs, systolic murmurs over aortic and mitral areas, lower edge of liver just palpable, B. P. 140/85, superficial lymph nodes and spleen not palpable, electrocardiogram normal, routine blood count, urinalysis, and serological examination of blood not remarkable or negative. X-ray of the chest (Figs. 12, 13) showed a mass in the mediastinum mainly to the right of the midline, esophagus displaced posteriorly and to right, and trachea displaced anteriorly and to right. Bronchoscopy showed no intrinsic lesion in trachea or bronchi. Left anterior scalene biopsy yielded a 5 mm. lymph node, histologically normal. On 8-10-54 the mass was removed surgically. It was located in the

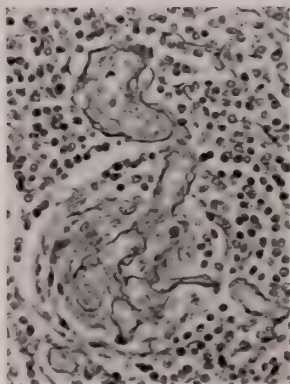


FIG. 19

FIG. 19. Case II—Follicle with ingrowing capillaries and conspicuous alteration of reaction center. Reticulum stain, $\times 210$.

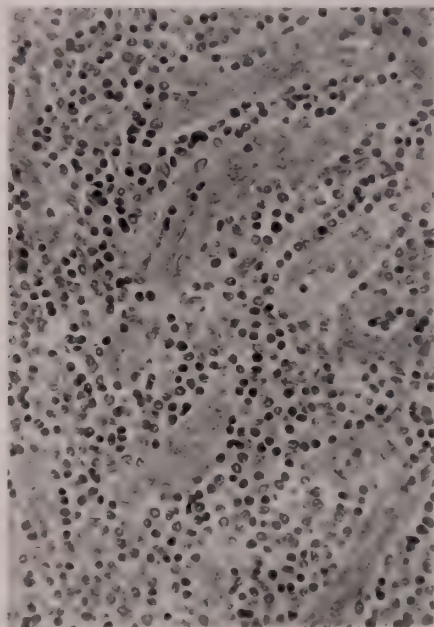


FIG. 20

FIG. 20. Case II—Interfollicular tissue showing lymphocytes and numerous capillary sprouts having plump endothelial cells, $\times 160$.

posterior superior mediastinum, lay between trachea and esophagus, and was attached to arch of aorta, trachea, esophagus, and superior vena cava. The surface was richly vascular, marked bleeding was encountered during removal, but it was removed readily. Inquiry as recently as Jan. 1957, 2½ years since operation revealed the patient in good health.

Pathology-Gross (Fig. 14). Mass measures 8 x 6 x 4 cm., weighs 150 gm., and is encapsulated. Fat and areolar tissue are focally adherent to the capsule. Cut surface is flat and pale brown.

Microscopic. In the capsule are hyalinized fibrous tissue, smooth muscle, elastic and reticulum fibers, large arteries, veins and lymphatics, and lymphoid aggregates having the structure of tiny lymph nodes. Hyalinized fibrous trabeculae extend through the substance of the specimen. Diffusely, but chiefly peripherally, are many lymphoid follicles of usual size, averaging a little less than 0.4 mm. in diameter (Fig. 15). The reaction centers appear as whorled nests of loose cells having large pale nuclei (Fig. 16); with the reticulum stain they are tangled nests of reticulum fibers, endothelial cells, and reaction center cells (Fig. 17). In only a few follicles are there unaltered or minimally altered centers. The majority show conspicuous transformation by the invading capillaries from the interfollicular tissue, carrying with them their reticulum and endothelial cellular components (Figs. 18, 19). The interfollicular tissue, which accounts for the bulk of the tumor, consists of broad cords or bands of small lymphocytes admixed with innumerable capillary sprouts. The capillaries, which in many areas constitute the predominant elements, are lined by plump endothelial cells and have small, often compressed and inconspicuous, lumens that may contain erythrocytes (Fig. 20). There is a very rich component of reticulum fibers, derived chiefly from the proliferated capillaries (Fig. 21). Small foci or fibrosis and diffuse moderate plasma cell and eosinophil infiltrations occur chiefly in the

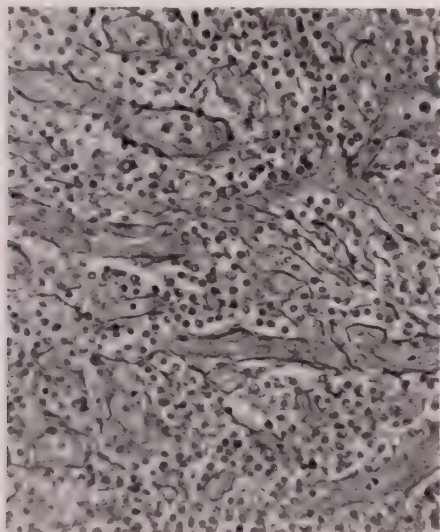


FIG. 21. Case II—Interfollicular tissue showing abundant reticulum fibers derived mainly from capillaries. Reticulum stain, $\times 210$.

cords, and hyalinized strands in the walls of the capillaries occur in the cords and follicles. No peripheral or central sinuses are identified in the lesion. No foreign bodies or crystals are observed.

MORPHOLOGICAL CONSIDERATIONS

Though there are notable differences in their morphology, the two lesions fundamentally appear similar. The essential structural features are marked proliferation of lymphoid and vascular tissues with penetration by capillaries of the lymphoid nodules (follicles). In the deltoid mass the lymphoid nodules are exceedingly large and abundant and constitute the dominant unit; in the mediastinal mass the cords dominate. As striking as the lymphoid tissue proliferation, is the enormous growth of blood vascular capillaries. These are found mainly in the internodular cords where, especially in the mediastinal lesion, their cells may be more numerous than the lymphocytes. The ingrowth of capillaries from the cords into the nodules is one of the most arresting features of both tumors and accounts for the altered, at times disrupted, nodules and distorted reaction (germinal) centers. The nests of larger cells in the lymphoid nodules are interpreted as reaction centers. They are more sharply circumscribed and the cells more whorled than in the reaction centers of most normal or hyperplastic follicles. But the location of the nests, cell type, and paucity of reticulum fibers in unaltered and minimally altered nests are quite in keeping with reaction centers. The whorled appearance is due, in part at least, to invasion by capillaries with resultant admixture of reaction center cells, reticulum fibers, and endothelial cells. An unusual feature in the deltoid tumor is the presence of multiple, as many as 6 or more, reaction centers in a single lymphoid nodule. It is felt that the most likely explanation is that the large lymphoid lobule or nodule really is a series of closely-set lymphoid follicles, each with its own reaction center. When the follicles merge or fuse, their boundaries cannot be defined and the appearance is that of one large nodule with multiple reaction centers. In the mediastinal tumor there is but one center to a lymphoid nodule, because each nodule is a single follicle rather than an aggregate of follicles.

NATURE AND ORIGIN OF LESIONS

Both lesions are well demarcated, generally encapsulated, have reaction centers in the lymphoid nodules, exhibit marked capillary proliferation, and show uniform cells and orderly pattern. Though there are many cells with large nuclei, no really atypical or bizarre cells are encountered. A small focus in the deltoid mass shows no capsule, but there is no evidence of aggressive or invasive tendency of the exposed lymphoid tissue into the adjacent muscle. The follow-up periods have not been long, 3 and 2½ years respectively, but there is no sign of clinical malignancy in either case. All of these features favor a benign tissue reaction, and we are so considering the lesions. Final judgment should be reserved until longer periods of follow-up are available. Are these lesions neoplasms or hyperplasias? The presence of lymphoid follicles and cords, persistence of reaction centers, pronounced proliferation of capillaries, and marked penetration of capillaries into lymphoid follicles favor a hyperplastic or reactive over a neoplastic lesion in

our view. In a series of mediastinal masses reported by Castleman and associates (2) the gross and microscopic features are quite similar to the mediastinal growth reported here. They considered their lesions benign, hyperplastic, and not of thymic origin. Our feelings are in agreement with theirs. Although the lymphoid tissue in our 2 lesions is organoid it is not possible to determine whether they were derived from lymph nodes because of the absence of demonstrable sinusoidal pattern. It is felt that the deltoid mass most probably did not arise in preexistent lymph node, and that the mediastinal mass did originate in a lymph node. The cause for the proliferation of the mass in the mediastinum is obscure. Examination of sections stained for acid-fast bacilli, other bacteria, and fungi were not revealing in this or the deltoid mass. Lymphocytic infiltrations in muscle may occur in various types of myositis, myasthenia gravis, rheumatoid arthritis, rheumatic fever, scleroderma, lupus erythematosus, dermatomyositis, a great variety of other disorders, and in apparently healthy individuals (3-5). By and large such infiltrations are felt not to be specific and generally do not form lymphoid follicles. None of these conditions was evident in the patient with the deltoid mass. The presence of crystals in the deltoid lesion is probably significant. Did the crystals incite the tissue reaction and are the whorled nests granulomas? The indiscriminate distribution of the crystals and absence of histiocytes, foreign body giant cells or fibrous tissue in the vicinity of the crystals suggest the possibility that the crystals themselves may not be inciting the tissue reaction. The only area where there is suggestive reaction to the crystals is in the centers of some of the follicles (Fig. 9), and to this extent such cellular aggregates may be considered granulomas. Crystals are not present in the majority of the centers, and we feel the latter are not granulomas but reactive centers in lymphoid follicles. We believe the crystals do indicate the probability that something had been instilled into the muscle, which could have been the injection of the immunizing agent. The nature of the crystals is at present unknown to us. We plan to study them further. Thus one wonders what role, if any, the immunizing intramuscular injection may have played in the development of the deltoid tumor. Local inflammatory reactions to injection of diphtheria toxoid, alone or in combination with other immunizing antigens, are not uncommon, and they may persist for several months. Reported studies of the local tissue changes are few, and those few reported do not indicate any pronounced growth of lymphoid tissue. The introduction of an antigen into tissues causes a local inflammatory reaction which may be dominated by lymphocytes (6). Organized lymphoid structures, lymphoid follicles and lymph nodes, may develop from small accumulations of lymphocytes, usually perivascularly, during embryogenesis of lymphoid tissue (7) and in chronic inflammation (8). Is it possible, therefore, that the injected material stimulated a lymphocytic response and that from the lymphocytic outpouring the large growth of organoid lymphoid tissue developed?

SUMMARY

Two cases of a large solitary growth of lymphoid tissue, of unusual structure, are reported, one in the deltoid muscle, and the other in the mediastinum. Marked proliferation of lymphoid follicles and capillary endothelial cells, peculiar

whorled reaction centers, and striking ingrowth and alteration of the reaction centers by the capillaries were the outstanding changes. The lesions are believed to be hyperplastic, probably inflammatory. The cause of the mediastinal mass is not known. The deltoid mass may possibly have formed in response to an injection of diphtheria-tetanus toxoid.

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PRIMARY PULMONARY HYPERTENSION AND THE PULMONARY VASCULATURE

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The number of cases designated as primary, idiopathic or solitary pulmonary hypertension, primary pulmonary arterial disease, primary pulmonary arteriosclerosis and related terms, appears to be increasing (1-11). The increase may be based on the more ready recognition through the use of cardiac catheterization, but the increase may be more than apparent since such cases had been identified before cardiac catheterization was introduced, and the lesions resulting from pulmonary hypertension have been known for many years (12-16). Most cases identified as primary pulmonary hypertension have been so diagnosed because of the absence of lesions commonly accepted as causes of pulmonary hypertension, namely, mitral stenosis, chronic left ventricular failure, pulmonary emphysema, pulmonary fibrosis or granulomatosis, kyphoscoliosis, pulmonary embolism or thrombosis, among others, rather than on the presence of particular clinical and laboratory observations. The clinical manifestations related to primary pulmonary hypertension have been regarded by some as characteristic enough to make the clinical diagnosis possible (5, 10). These usually include, in decreasing order of frequency, (a) a history of prolonged and often progressive exertional dyspnea, (b) fatigue, (c) syncope, (d) thoracic pain, particularly on effort, (e) cyanosis, (f) cough, and (g) dependent edema. Orthopnea, paroxysmal dyspnea, and hemoptysis are usually absent. However, other investigators have considered these manifestations to resemble so closely those of patients with some types of secondary pulmonary hypertension, that a clinical diagnosis of primary pulmonary hypertension would be difficult (8).

In recent studies, primary pulmonary hypertension has been reported to occur predominantly in women and most patients have been under forty years of age. All eight patients in our study were women (8, 26). Thus far, no relationship to pregnancy or menstruation has been established, but has been suspected.

There is agreement on the pathogenesis of many of the lesions observed in advanced primary pulmonary hypertension. Those of the heart and major branches of the pulmonary arteries are accepted as the result of the pulmonary hypertension. The heart is enlarged to two to three times its expected weight with hypertrophy and dilatation of the right ventricle. The pulmonary artery and its major branches are dilated. Intimal thickening with atheromatosis is the rule, with this alteration much more advanced than expected for the patient's age. The walls of the elastic arteries, namely the pulmonary artery and its major branches are,

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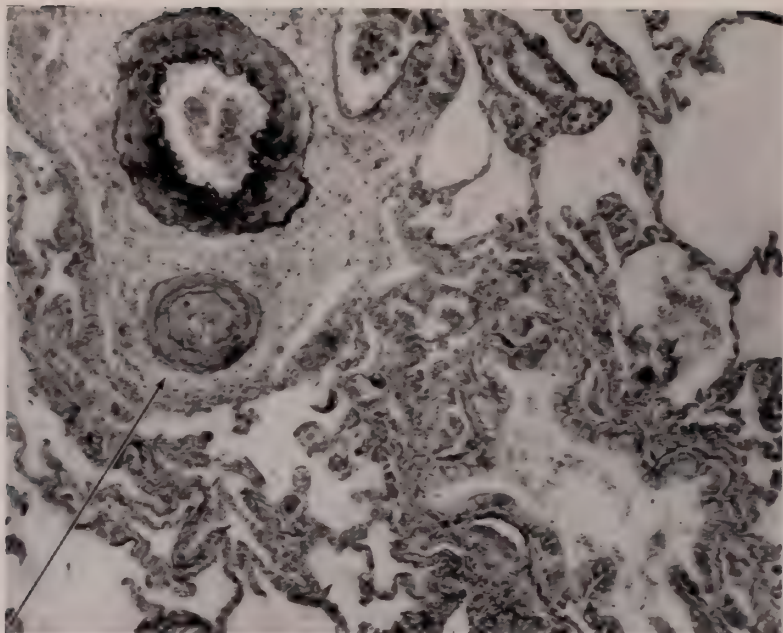


FIG. 1. There is thickening of the intima and duplication of the elastic laminae in the smaller artery (see arrow). Elastic tissue stain. (By permission of the American Journal of Medicine, reference 8, case 4).

however, thinner than normal with reduction in the muscular component of the wall.

Intimal thickening without atheromatosis is common in the smaller, or muscular arteries (Fig. 1). In these arteries, there is reduction in the muscular component, but it is usually focal, and this may be accompanied by an interruption and or loss of the elastic laminae. On the basis of our own experience, this alteration may be the end result of a focal necrosis due to arteritis, this term being used to indicate a tissue reaction to injury, which under these circumstances might be primarily mechanical. The pathogenesis of these lesions and their relationship to pulmonary hemodynamics and other arterial lesions, e.g. thrombosis, are subjects of current discussion. In smaller arteries and their branches, we have observed an arteritis with the morphologic features of polyarteritis nodosa (Figs. 2, 3). A long duration of the process is suggested by the presence of several stages of an arteritis being recognizable. The lesions have been limited to the lungs, have not been numerous and in the absence of other evidence for these being part of a generalized arteritis or granulomatous process, they have been interpreted as sequelae of the pulmonary hypertension and not antecedent to it. Medial necrosis was reported in two of four cases described by Heath, Whitaker and Brown (2), and Shepherd, *et al* (1) mentioned necrotizing arteritis in one of three fatal cases. In our belief that this lesion is an effect of pulmonary hypertension, we are in agreement with Edwards (1, 17) and Liebow (18), among others. A different relationship between such vascular lesions and pulmonary

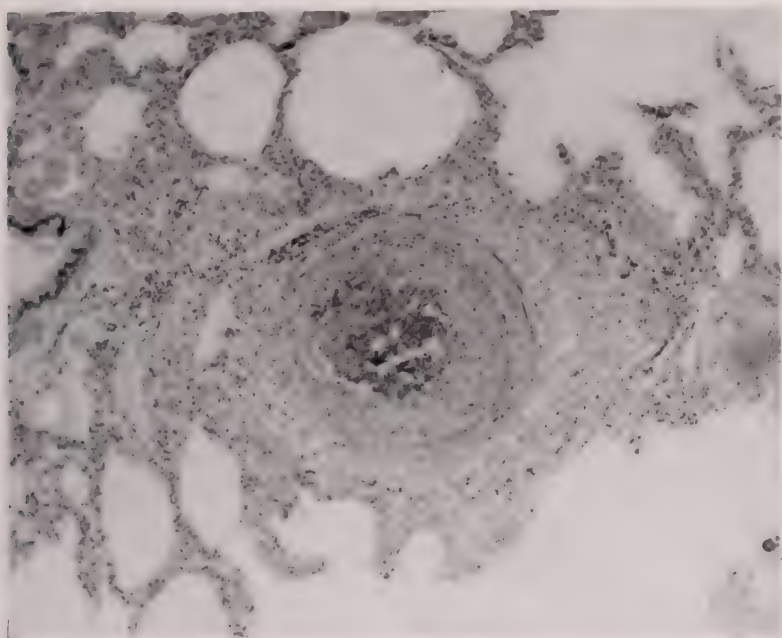


FIG. 2. Acute arteritis with thrombus. Hematoxylin and eosin stain.

hypertension is implied by use of the term "periarteritis nodosa" when this association has been observed in patients with mitral stenosis (19). According to Rose and Spencer (20), polyarteritis nodosa and the arteritis associated with pulmonary hypertension "are quite distinct, and that to use the term 'polyarteritis nodosa' for the pulmonary arteritis associated with pulmonary hypertension leads only to confusion." Instances of necrotizing arteritis involving the lungs in patients with pulmonary hypertension due to mitral stenosis and congenital heart disease have been described and cited by Edwards (17). Pulmonary arteritis has been reported in advanced mitral stenosis by Spain (21) who regards pulmonary hypertension as the pathogenetic basis for this lesion.

The relationship of pulmonary hypertension and increased pulmonary vascular resistance to pulmonary arterial lesions appears as complex as the relationship of systemic arterial hypertension to systemic arterial lesions. With comparable levels of systemic arterial hypertension in the dog, one method, e.g. "neurogenic" hypertension, results in no acute arterial lesions (22), whereas another, e.g. administration of adrenalin, N-amylamine or pressor extracts of normal hog kidney, result in acute arterial and arteriolar lesions (23). Other components of the response to acute hypertension as studied by Waters (23), appear to be factors as important as the hypertension itself in the production of acute systemic arterial lesions. The rapidity of the increase in arterial pressure may be a determinant in the nature of the arterial lesion produced, in the systemic as well as the pulmonary arterial circulation. In Waters' experiments, and in those of Ferguson, Berkas and Vareo (24) which involved anastomosis of a systemic artery

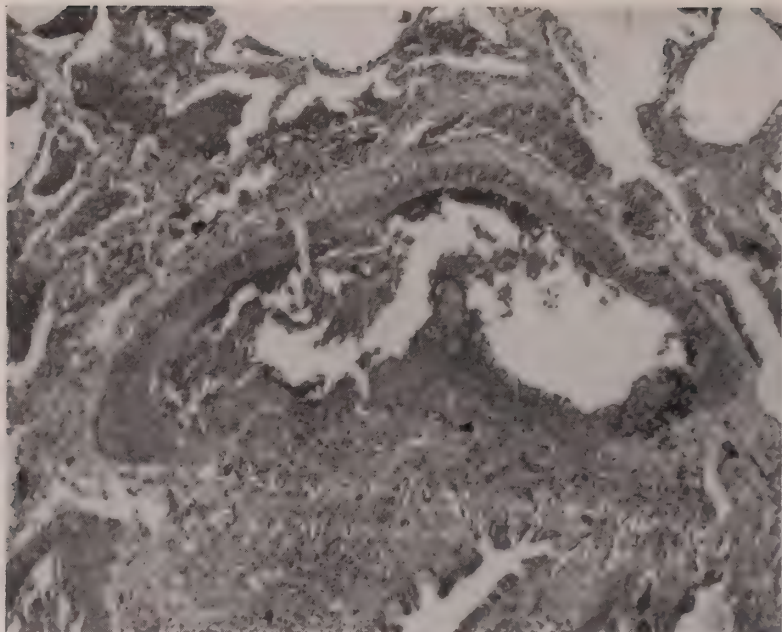


FIG. 3. Acute arteritis with fibrinoid deposits in arterial wall and periarterial cellular infiltration. The portion of the artery occupying the upper half of the field is normal. Hematoxylin and eosin stain. (By permission of the American Journal of Medicine, reference 8, case 3).

to a pulmonary artery, rapid increases in arterial pressure resulted; in the former, acute arteritis occurred in the systemic circulation, in the latter, in the pulmonary circulation. Pertinent sequential studies of alterations in the pulmonary arteries related to pressure modification were carried out by Dammann, Smith and Muller (25).

If the basis for pulmonary hypertension is neuro-humoral, then this stimulus may also be a factor in the pathogenesis of the arterial lesions, which if progressive may become irreversible.

By producing vascular obstruction such lesions may result in a pulmonary hypertension which no longer requires the initial stimulus for its persistence. One reason for suspecting such a mechanism is the nonspecificity of the pulmonary arterial lesions observed in primary pulmonary hypertension; essentially all have been observed under conditions known to result in pulmonary hypertension, and no anatomic abnormality appears to be the pathogenetic basis for all cases. In this connection, however, arteriographic studies as performed by Evans, Short and Bedford (3) who have suspected an "arterial achalasia", should be pursued.

Another lesion reported in many cases of pulmonary hypertension and observed in our own, also involves the smaller arteries and arterioles. It consists essentially of an endothelial proliferation which we regard as secondary to degenerative mural alterations related to the pulmonary hypertension. These have been considered to be organized thrombi, arteriovenous communications and glomus-like lesions. We have applied the term "plexiform lesion" to this

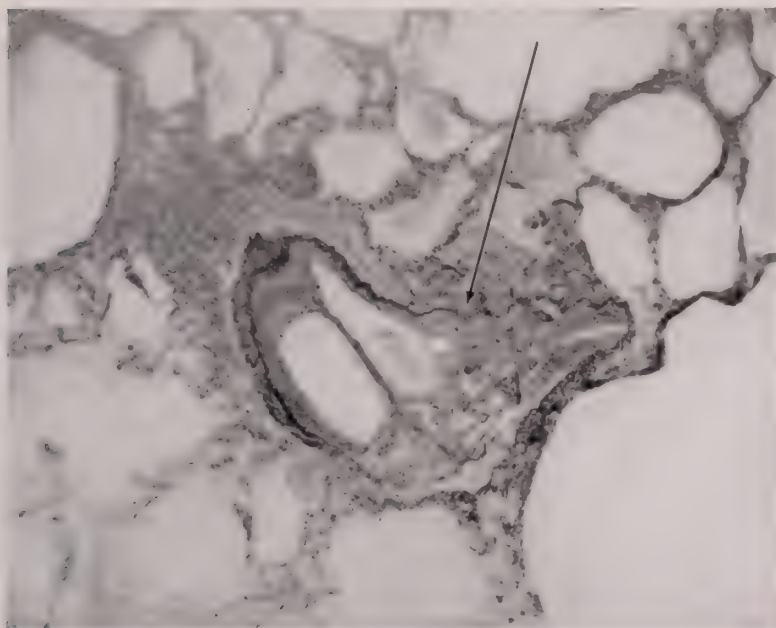


FIG. 4. Artery with intimal thickening and disruption of elastic laminae. Arrow points to defect in elastic lamina; to the right there are elastic fiber fragments. Elastic tissue stain.

alteration, a term used by Edwards (17) with whose interpretation we are in agreement. Step sections have demonstrated for us that the vascular abnormality occasionally associated with the plexiform lesion is an arteriolar-capillary communication resulting in a sinus-like vascular formation (Figs. 4-6). The plexiform lesion, arteriolar-capillary communications and sinus-like vascular formation we regard as resulting from degenerative changes produced primarily by the pulmonary hypertension. Such lesions have also been observed in cases of patent ductus arteriosus and ventricular septal defect (17). We have observed them in advanced mitral stenosis but, thus far, not in the absence of known or suspected pulmonary hypertension.

As mentioned above, there is evidence that all of the lesions of the pulmonary arteries described thus far, (a) the dilatation of the pulmonary artery and its major branches with intimal thickening, atheromatosis and atrophy of muscular components of the media, (b) acute arteritis with morphologic sequelae in the form of focal atrophy of the media involving the muscular and elastic fibers, and (c) the plexiform lesion with endothelial proliferation, and (d) the arteriolar-capillary sinus-like formation, result mainly from pulmonary hypertension, and have been observed in secondary as well as primary pulmonary hypertension.

Two more controversial aspects remain: (a) the relationship of thrombi in the pulmonary arterial circulation to pulmonary hypertension and (b) the possible anatomic or other basis for the pulmonary hypertension in cases we currently classify as "primary".

In eight cases of primary pulmonary hypertension which we have studied re-

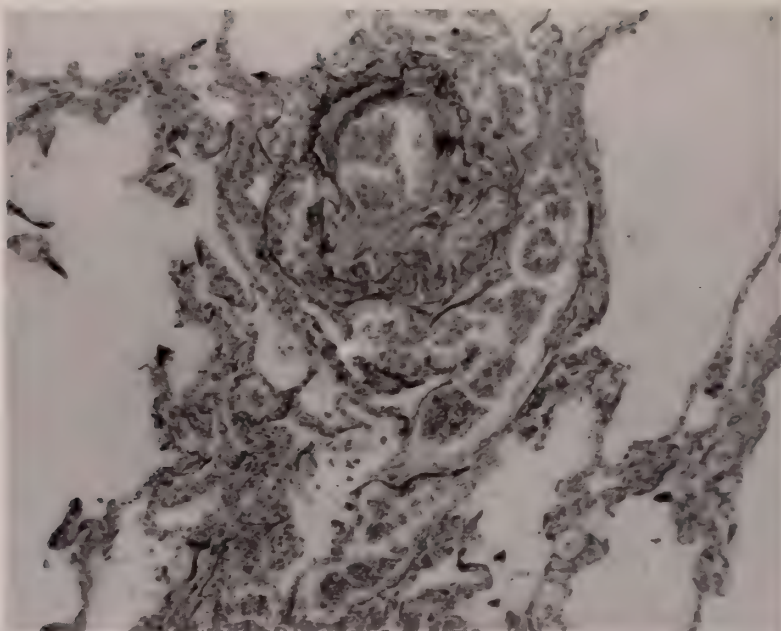


FIG. 5. The lower portion of the artery lacks elastic laminae and has multiple vascular communications with alveolar wall capillaries. Elastic tissue stain. (By permission of the American Journal of Medicine, reference 8, case 4).

cently (8, 26), thrombi of various sizes were observed in five. Some thrombi were noted in association with an arteritis involving the smaller muscular arteries (Fig. 2), and some with plexiform lesions in arterioles. In other words, thrombi occurred at sites of injury or alteration of the vessels involved. Other thrombi, usually in the larger arteries, had no association with vascular injury and may have had their origin as emboli. Thrombosis of the larger systemic veins is expected in prolonged pulmonary hypertension, particularly with right ventricular failure, and embolization of the pulmonary arteries also expected. However, as Shepherd et al (1) have observed, a thrombus in the pulmonary arteries suspected of being an embolus because of the normal appearance of the arterial wall at that site, may actually be thrombus propagated from a site of autochthonous thrombosis due to an arteritis occurring on the basis of pulmonary hypertension. This is not to contradict evidence obtained in man and the experimental animal, that pulmonary hypertension may follow an obstruction of the pulmonary artery and its branches, by emboli, injected clot or plastic spheres (27). It is mentioned to point out that thrombi observed in the pulmonary arterial system in cases of pulmonary hypertension, may occur on the basis of vascular alterations of these arteries produced by the pulmonary hypertension, e.g. atherosclerosis, arteritis, etc. These alterations differ from those which may be produced by the lodgment of an embolus. We have noted a cellular inflammatory reaction in the wall of the pulmonary artery with increased vascularity at the site of attachment of an embolus but have not seen fragmentation, distortion and loss of elastic fibers which characterize the lesion referred to above as arteritis.

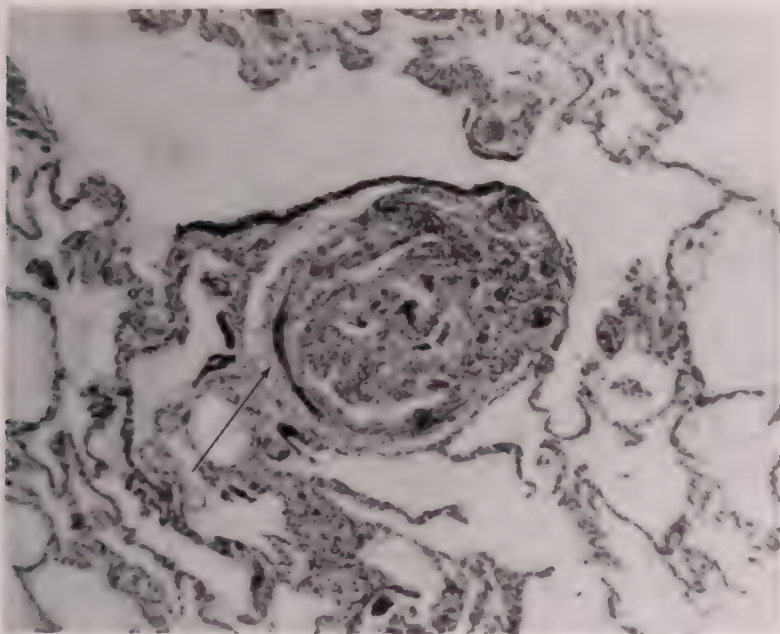


FIG. 6. Defect in the media with (1) loss of muscle fibers, (2) plexiform lesion and (3) multiple arteriolar-capillary communications. Arrow points to only muscle fibers identifiable in the wall of this artery. Trichrome stain. (By permission of the American Journal of Medicine, reference 8, case 4).

Finally, is there an anatomic or other basis for pulmonary hypertension which currently does not fall into any of the categories considered to be responsible for secondary pulmonary hypertension? If there is not, then terms such as primary, idiopathic or solitary can be applied appropriately to the cases under discussion. In some studies such terms have been used, but the implication made that the presence of a muscular coat in the wall of the arteriole (less than 100 microns in external diameter) may be the anatomic basis for the hypertension (2). The presence of a muscular media in arterioles of this size has also been mentioned in other recent publications and the lesion described as primary pulmonary arterial or vascular disease (6, 9). In cases with this alteration, there has been clinical and anatomic evidence of the pulmonary hypertension. Not all cases of primary pulmonary hypertension have pulmonary arterioles containing a muscular media. In our eight cases, this was observed in four (Fig. 7). In none of the eleven cases of Evans, Short, and Bedford (3) was a muscular coat found between the two elastic laminae of the arterioles, whereas it was found in the three cases of Heath, Whitaker and Brown (2). The lesion has been described in cases of Eisenmenger's syndrome by Edwards who regards it as a persistence of the fetal type of pulmonary arteriole. Perhaps, the presence of an arteriolar muscular coat separates such cases from the group diagnosed as primary pulmonary hypertension. However, it is apparent from the arteriographic studies of Evans, Short and Bedford (3) who noted no arteriolar muscular coat, that there are other structural abnormalities which are responsible for narrowing in the distal

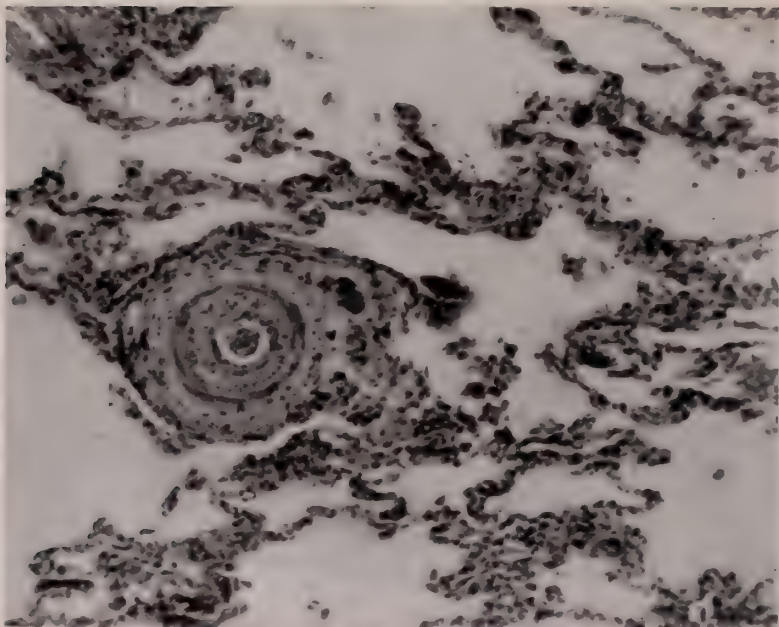


FIG. 7. Prominent muscle fibers in an arteriole in which there is no thickening of the intima. Trichrome stain. (By permission of the American Journal of Medicine, reference 8, case 1).

branches of the pulmonary arterial tree. Vascular obstruction was demonstrated histologically and arteriographically in nine of their eleven cases. In the other two, there was a normal histologic pattern despite obstruction being demonstrable by arteriogram, suggesting "arterial achalasia". Wade and Ball (5) believed the major alteration to be abnormally contracted small muscular arteries and the basis for obstruction of the pulmonary arterial flow. Such an abnormality might be the basis for pulmonary hypertension, with all of the lesions mentioned above, including the presence of an arteriolar muscularis, being the result of the pulmonary hypertension. The pulmonary hypertension would become increasingly severe as lesions such as intimal proliferation developed to produce progressively more vascular obstruction. Such an explanation appears acceptable even though the reduction of pulmonary arterial pressure by tolazoline hydrochloride (Priscoline) suggests that the neural and/or humoral mechanisms may be factors in the pathogenesis of pulmonary hypertension (4, 5). Dresdale (10, 28) has observed also that anoxia-induced pulmonary hypertension is not influenced by tolazoline hydrochloride. There may be a single mechanism responsible for pulmonary hypertension capable of being activated by a number of stimuli, e.g. reduced oxygen tension, increased left atrial pressure, etc. It is apparent that the arterial and alveolar wall alterations observed in mitral stenosis are not of such a type and degree as to be the anatomic basis for the pulmonary hypertension associated with this valvular lesion (29) and, furthermore, surgical correction of mitral stenosis leads to a reduction in pulmonary arterial resistance

and pressure. The nature of the ultimate process responsible is not known; pulmonary hypertension is reduced only transiently by tolazoline hydrochloride and is little affected by hexamethonium and bilateral sympathetic block (5). It would still appear, however, that the most promising information regarding the pathogenesis of pulmonary hypertension might be expected from studies of the neural and/or humoral control of pulmonary arterial blood flow.

SUMMARY

A review of recent work on primary pulmonary hypertension has produced evidence that this unusual syndrome should continue to be regarded as an entity. No anatomic alteration which might be considered as pathogenetic is common to all cases. Essentially all lesions observed can be interpreted as morphologic representations of the effects of pulmonary hypertension, although additional factors may be operative. Arteriographic, histologic and catheterization studies identify the major abnormality as an obstruction in the smaller arteries and arterioles. Data which may ultimately explain the pathogenesis of what we must currently term primary pulmonary hypertension, should be sought in studies of neural and/or humoral mechanisms which control the pulmonary circulation.

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MOTIVATION AND GOALS IN MEDICINE IN MID-TWENTIETH CENTURY

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My dear young colleagues:

In spite of the presence here this morning of the Dean and distinguished members of the faculty, I shall address myself entirely to you, for this is YOUR DAY. I feel proud and privileged that I have been chosen to guide your earliest footsteps as neophytes in the profession of medicine. I stand before you in reverence and humility, for sitting there among you, as yet unknown and unrecognized, may be the Ehrlich, Pasteur or Lister of your generation.

Custom has decreed that the *commencement* orator have a wide latitude in his choice of subject. The general atmosphere of graduation with the knowledge of a job well done, even permits him to cast his address in a satiric or humorous vein. Thus it was that the title of a recent class day oration at an older medical school was "Lavender and Old Lucite." But I beg you, here at the threshold of your careers, to permit me to be more serious, although I hope not too boring.

Your predecessors on these benches have the distinction of being in the first class in this school, but after several decades this distinction will gradually lose its sharpness of focus, and members of the first two or the first five classes will feel an equal pride in their place as the pioneers in a great undertaking. How great this will be depends both on you as students and on us as your teachers. We are tied together now in an indissoluble union which succeeds only when each partner contributes all within his or her power to its success.

All of you, no doubt, when interviewed for admission to this as well as other schools of medicine, were asked to give your reasons why you wished to choose medicine as a career. By virtue of the efficiency of the grapevine system, the question is usually anticipated. However, in spite of much searching of soul, many candidates are unable to bring to consciousness the specific motivating forces that have led them to decide upon medicine as a calling. I have myself frequently witnessed the embarrassment of candidates, and the eventual somewhat shame-faced recitation of an obvious stereotyped answer, which usually consists of two parts: (1) I like to work with people, and (2) I am good in science. And yet, these seemingly studied responses appear to encompass for most of us a profound idealism, however lamely expressed, and an almost irresistible urge which leads many aspirants to accept untold hardships and the severest kind of deprivation to achieve their goal.

Recently Dr. Noah D. Fabricant (2) collected in a little book the expressed motivations for becoming doctors of a number of distinguished and articulate

Address to Second Entering Class, Albert Einstein College of Medicine, Yeshiva University, September 17, 1956.

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physicians, which I would recommend for your perusal. From these autobiographical confessions, it is apparent that a variety of precipitating factors is responsible for the final decisions to enter the medical profession. Sometimes it is only because a child is brought up in a medical atmosphere where one or even both parents are physicians, and he cannot think of himself in any other career. At other times it may be a purely accidental experience. Thus Freud (3) related that on hearing a professor at the university read Goethe's essay on "Nature," in which he pictured her as a bountiful mother who allows her favorite children the privilege of exploring her secrets, then and there decided to become a doctor.

Sometimes the choice is made by exclusion of other careers. Hans Zinsser (4), for example, who had many talents, had considered writing or biology among others, but eventually settled on medicine and "always held that medical training has for certain types of people a ripening influence that no other field of education possesses. Aside from the habits of hard work that it demands, it embraces a broad survey of the biological field, enforces a considered correlation of the fundamental sciences, and on the human side, brings the thoughtful student face to face with the emotional struggles, the misery, the courage and cowardice of his fellow creatures—to say nothing of the familiarity it gives with sociological conditions, vice, crime and poverty. There is in it a balanced education of the mind and spirit which, in those strong enough to take it, hardens the intellect and deepens the sympathy for human suffering and misfortune."

W. Somerset Maugham (5) who, from childhood, wanted to be a writer and used medical registration merely as a "chance of living" in London and so gaining the experience in life that he hankered for, nevertheless wrote with enthusiasm about his medical experience and especially his spell of duty as a student in an emergency ward. "For here," he said, "I was in contact with what I most wanted, life in the raw. In those three years I must have witnessed pretty well every emotion of which man is capable. It appealed to my dramatic instinct. It excited the novelist in me. Even now that forty years have passed I can remember certain people so exactly that I could draw a picture of them. Phrases that I heard then still linger in my ears. I saw how men died. I saw how they bore pain. I saw what hope looked like, fear and relief; I saw the dark lines that despair drew on a face; I saw courage and steadfastness. I saw faith shine in the eyes of those who trusted in what I could only think was an illusion and I saw the gallantry that made a man greet the prognosis of death with an ironic joke because he was too proud to let those about him see the terror in his soul."

Frequently upon questioning candidates in an interview for admission to this school, as to why they happened to choose medicine for their life's work, I have had the feeling that they would like to reverse the situation and ask the same question of me. I have thought much upon it in the preparation of this address. It seemed to me that I have "always" wanted to be a doctor, but upon reflection I was able to trace to one incident in my early childhood the beginnings of this determination. I was born in Latvia, which was then a part of the Czarist Empire of Russia. We were a poor family with nine children, but in many ways more fortunate than our neighbors in that we were all sound of mind and limb. The incident occurred when I was about five years of age. My oldest sister who

was then a strong, healthy girl of 16, spat up some blood one morning. Now it must be remembered that among ghetto Jews in old Russia the great killer was not, as in present-day America, heart disease or cancer, but consumption, that is pulmonary tuberculosis, and spitting of blood was one of its most obvious symptoms. My parents were naturally paralyzed with fear, and transmitted this fear even to the youngest of us. With many tears and forebodings, it was decided to take her to Dr. Krueger, the kindly old German physician. None of us was quite as frightened as the girl herself, and the trip from the valley where the Jews lived to the doctor's house at the top of the hill was almost beyond her strength, and she was practically carried there by my distraught father and a sturdy older brother. The doctor was wise in his ways, examined the situation thoroughly, and at last pointed out to my sister and my father that the blood came from an inflamed gum and that her lungs were as sound as ever. The tragedy was immediately transformed into joy and my sister came bounding home, as my mother often told it, like a young doe (*wie ein junger Hirsch*).

Sometimes the motivation may be the very prosaic one of a way of earning a decent livelihood. In occasional cases it may be illusory dreams of wealth or glory. Here I may say parenthetically that any doctor worth his salt can earn it, but he who seeks only for wealth and glory as such had better enter another profession. In any case, however diverse the motivation, to succeed in a medical career one must come back to the formula of the medical candidate, to "love to work with people" and to "be good in science."

He must also bring to his work what Dr. John Brown (1) has called "genius and sense." By the former he meant a "peculiar native aptitude" like a "genius for governing or killing or for curing the greatest number of men . . .," and "sense" implies "exactness and soundness, power and promptitude of mind." If one lacks these qualities, he continued, "a young medical student may have zeal, knowledge, ingenuity, attention, a good eye and a steady hand—he may be an accomplished anatomist, stethoscopist, histologist, and analyst; and yet, with all this, all the lectures, all the books, and all the sayings, and all the preparations, drawings, tables, and other helps of his teachers, crowded into his memory or his notebooks, he may be beaten at treating a whitlow or a colic by the nurse in the wards where he was clerk, or by the old country doctor who brought him into the world and who listens with such humble wonder to his young friend's account, on his coming home after each session, of all he had seen and done—of all the last astonishing discoveries and operations of the day."

But for you who are registering in medical school today, the die is cast, however you arrived at a decision. What have you to look forward to in the next four years, and after that, for the rest of your lives?

For one thing we can promise you not only a richer but also a more pleasant life as medical students than was true only a few generations ago, when medical schools were proprietary institutions and a professor's rewards came in fees paid him by individual students, ergo—the more students, the more fees. A famous New York physician, Dr. Charles F. Gardiner (6) who died only nine years ago, described his first days at a sister institution in this city in 1875 as follows:

"The lecture room was in the form of a pit and here before a table sat the

Professor while all around were long tiers of wooden benches extending upward and backward nearly to the ceiling. The light was dim, the whole place dusty and littered with cigarette stubs and matches, the air so hot and foul that frequently students fainted. The tobacco smoke rolled up to the roof like a dense fog, and it was only with an effort one could breathe. Eight hours of this on hard benches muddled my brain so that I could not think. The students lounged on the seats, rough, untidy, their feet on the backs of the benches in front. Cat calls, whistles, and yells greeted the professor and often interrupted his lecture; feet stamped thunderously on the bare floor and dust flew up to mingle with the tobacco smoke. The lecture was given in the precise and deadly manner common at that time. The steady voice droned on hour after hour in bald scientific statements with not a gleam of spirit or a hint of humor, a deadly monotony so dry and wearisome that at last the exhausted brain refused to register."

Lest you think, however, that no voice was raised in protest against such methods, listen to Sir William Osler (7) in his address at McGill College in 1891: "... the problem of all others which is perplexing the teacher today is not so much what to teach, but how to teach it. . . . All will agree that a large proportion of the work of a medical student should be in the laboratory and in the hospital. The dispute is over the old-fashioned lecture which has been railed against in good set terms, and which many would like to see abolished altogether. It is impossible to make a fixed rule, and teachers should be allowed a wide discretion. Slowly but surely practical methods are everywhere taking the place of theoretical teaching, but there will, I think, always be room in a school for the didactic lecture. It is destined within the next ten years to be much curtailed, and we shall probably, as is usual, go to extremes, but there will always be men who can present a subject in a more lucid and attractive manner than it can be given in a book."

It was fascinating to recognize these very problems, arising in the discussions preliminary to and those still continuing, facing the members of your faculty in establishing the teaching philosophy of this school.

Today, in many schools, the extremes against which Osler cautions us are riding rampant, but at our institution we have decided to follow his wiser dictum of allowing our teachers wide discretion in the way in which they present their material.

We are, however, again becoming concerned about what to teach. The body of medical knowledge in the past twenty-five years has become so great that more and more segments of it have split off to form highly specialized fields of endeavor. As each new specialty developed, its zealous acolytes demanded a special department, a professorial chair and innumerable hours in the medical school curriculum. About fifteen years ago, this process had reached a point of supersaturation so that the addition of so much as one extra pause for breath threatened to burst the entire curricular structure. Everybody almost simultaneously realized that you cannot turn a medical student into an experienced physician in four years, and the effort to stuff him with facts like cramming corn into a Strasbourg goose therefore became an absurdity. President Kirk (8) of Columbia University summarized the situation by stating that: "As the totality of knowledge ad-

vances, the natural tendency is merely to add the new unto the old, increasing the number of courses and the length of time demanded of a student until the luckless neophyte is drowned in a sea of data."

He quotes a committee report to the effect that the advantage of intellectual power over information is that "it enables the possessor to continue his education and enlarge his knowledge. . . . Knowledge is expanding so rapidly that it is impossible to give a man all the knowledge he will need, and the effort to do so is certain to fail. . . . Each student, in his own way, and to the limits of his increasing powers, must be a searcher of the truth no less than his teacher, and must be aided to develop a capacity which can be utilized throughout his life."

We are resolved that these shall be our educational aims at the Albert Einstein College of Medicine. The word "educate," after all, is derived from the Latin root *educere*, which means literally to lead forth.

But something in addition to what to teach and how it is to be taught is also changing, and that is the interrelationship between faculty and student. It is not so long ago when in the medical schools of our country, an opening lecture such as this one would have contained the ominous threat that before the end of the first year, at least a third of the class would be failed, and by the end of the second year the bright young hopes of 20 per cent more would have withered. Very little thought was given to the qualifications of students before admission in those days, and the successful finalist reached Commencement Day by a process of the survival of the fittest, or, perhaps better, the toughest.

This led to extreme competitiveness, jealousies, distrust, secrecy and dishonesty among the students, and an insurmountable wall between them and the faculty. The primary aim was to stay aboard, even if this meant stamping upon the prostrate forms of less fortunate or less ruthless fellow students. Passing examinations with the highest grades became paramount and exceeded in importance learning for its own sake.

Today we pick out winners by a more difficult process, namely careful selection *before* admission. This is how you have been chosen, and having chosen you in this way, yours are precious lives to us; we are betting on you. We believe that in this school we have gone further along this path than many of our sister institutions, in that beyond the highest standards of character and scholarship, we have no other qualifications and restrictions. For while most schools now use similar basic criteria for the selection of students, many of them are limited by special quotas. Thus state schools are limited largely to in-state candidates; many private schools, on the other hand, insist on a wide geographic representation. It has been stated facetiously about one large Eastern college that in order to be certain of admission to it, all one has to do is have a minimal intelligence quotient of 90 and come from Wyoming.

I have addressed you as "my dear young colleagues." This is no empty phrase. We want to work together with you and will expect you to work cooperatively with each other. And while it is anticipated that you are here to receive an education in medicine, we also expect that your fresh minds and youthful energies will fertilize and enrich our minds in turn.

It is not going to be easy, but we promise that you will love it, or hate it so

violently that you will hastily quit. We cannot even promise you that you will be free from examinations but their purpose will be to let you know how well you have grasped the subject in hand rather than to rate you one-tenth of one per cent above or below some fellow student in rank. You will be assigned to a faculty advisor along with a few other students, to form one of a number of small academic family groups, but you will have easy access to every member of the faculty from the dean to the youngest instructor. You may often be confused and disheartened by all you must and want to learn, until you discover that your cleverest and most experienced professors are sometimes also dismayed and discouraged by how little they know and by how much there is still to learn.

The medical profession is unique in many ways, but mostly because the potter and the clay are made of the same material. When dealing with patients, you must never forget that but for the grace of God you might be occupying the bed next to his, if not now, then perhaps tomorrow. And when you find yourself some day elevated to that awful-lonely peak, one step below the footstool of God, when a life hangs in the balance depending upon your decision, derive comfort by asking yourself what you would want to have done if you were in that patient's place, and then do it by God and with a clear conscience.

You will have a right to feel yourselves fully inducted into our profession not when you have received your diplomas, but when you have thoroughly understood how fine is the thread by which this mysterious thing called life is suspended.

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DISTURBANCE OF HEMOSTASIS IN RABBITS TREATED WITH POLYVINYL PYRROLIDONE (PVP)^{1, 2}

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In the course of investigations of biologic effects of polyvinyl pyrrolidone (PVP) (1, 2) it was noted that rabbits which had received repeated injections of PVP showed abnormally long bleeding from venipuncture wounds. This observation led to systematic studies on the effect of polyvinyl pyrrolidone on bleeding time, platelet count and related factors involved in hemostasis of rabbits. A preliminary report of this work was presented in 1954 (3). Coagulation time, prothrombin time as measured by the one-stage method of Quick, fibrinogen, red cell count and other hematologic findings were not significantly affected. However, a prolonged bleeding time and thrombocytopenia developed after sufficient dosage of PVP. The general health of the animals was not impaired unless intercurrent infections set in. The weight remained constant, or gain in weight occurred in younger animals.

MATERIALS AND METHODS

In healthy male albino rabbits weighing from 2,500 to 3,500 Gm. prior to administration of PVP, baseline values were obtained for the following hematologic tests: venous bleeding time, for which a lateral ear vein was utilized; platelet count both by direct count (Reese and Ecker) and by indirect count in a smear (Fonio); coagulation time (Lee and White); total red cell count; prothrombin time (one stage method of Quick). In later experiments determinations of fibrinogen and of clot retraction time were included. PVP preparations of two different molecular distribution were used: K33 and K84.³ K33 signifies a PVP preparation with an average molecular size of 35,000 to 40,000, whereas K84 indicates one of around 150,000. Small fractions of much higher, and lower, molecular weights are also present in both preparations. Three and one-half per cent solutions of PVP were prepared in saline and autoclaved. Fresh solutions were prepared at least once weekly. Intravenous or subcutaneous injections were given. Each single injection contained 0.35 Gm. of PVP per Kg. of weight of the rabbit.

RESULTS

Changes in platelet count and bleeding time. The results obtained in 10 rabbits which were injected with varying amounts of PVP of the two different molecular

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³ The PVP preparations were made available through the courtesy of Dr. D. B. Witwer, General Aniline and Film Corporation, New Jersey.

TABLE I
Effect of PVP on hemostasis

Rabbit No.	Period of Administration	PVP (Gm.)		Date of Tests	Platelets* (10 ³ per cu. mm.)	Bleeding Time† (secs.)	Serum PVP (%)
		K 33	K 84				
101	3/16-4/29	18.0					0.31
	5/25-6/22		14.1	6/25	40	660	1.56
102	3/16-4/29	20.0					
	5/25-6/22		16.7	6/25	51	720	0.90
126	9/14-9/27		10.5	10/1	112	195	0.78
127	9/14-9/27		8.7	10/8	120	220	0.84
128	9/14-9/27		8.6	10/8	108	315	0.85
	12/2-12/6	4.7		12/14	95	334	0.54
131	9/14-9/27		8.0	10/8	210	195	0.70
130	1/11-2/26	12.5					
	3/8-3/12		3.2	3/16	130	1540	0.97
104	1/11-2/26	18.2		3/2	308	186	0.32
	3/10-3/12		4.7	3/16	302	252	1.05
				3/23	62	1450	0.85
105	1/11-2/26	18.8					
	3/8-3/12		4.8	3/16	160	380	1.29
129	1/11-2/26	17.8					
	3/8-3/12		4.5	3/16	200	310	0.90

* Normal range: 200-600 Mean: 330 ± 77

† Normal range: 30-125 Mean: 73 ± 26

distributions, are summarized in Table I. The first abnormal results obtained after administration of the recorded quantity of PVP are listed. The ranges, means and standard deviations of platelet counts and venous bleeding time obtained in 30 normal rabbits are recorded at the bottom. Deviations from the norm occurred in two tests only: the bleeding time was prolonged and the platelet count was depressed. The changes in these two tests were not always entirely parallel. In some cases slight prolongation of the bleeding time was not associated with a diminished platelet count. On the other hand, the diminished platelet count persisted in some animals for a longer time than prolongation of the bleeding time. The only other test showing abnormal findings was the clot retraction in animals with reduced platelet counts.

Effect of molecular size of PVP

It is apparent that PVP of the larger molecular size (K 84) was much more effective than was K 33 in prolonging the bleeding time and reducing the platelet count. Of 4 animals (130, 104, 105, 129) injected first with doses of PVP ranging from approximately 12 to 19 Gm. of K 33, only one (*104), showed a slight extension of the bleeding time. On the other hand, all four rabbits (126, 127, 128, 131) injected first with K 84 showed abnormalities of greater or lesser extent following administration of from 8 to 10.5 Gm.

Preceding administration of K 33 enhanced the subsequent effect of the K 8

RABBIT NO. 130

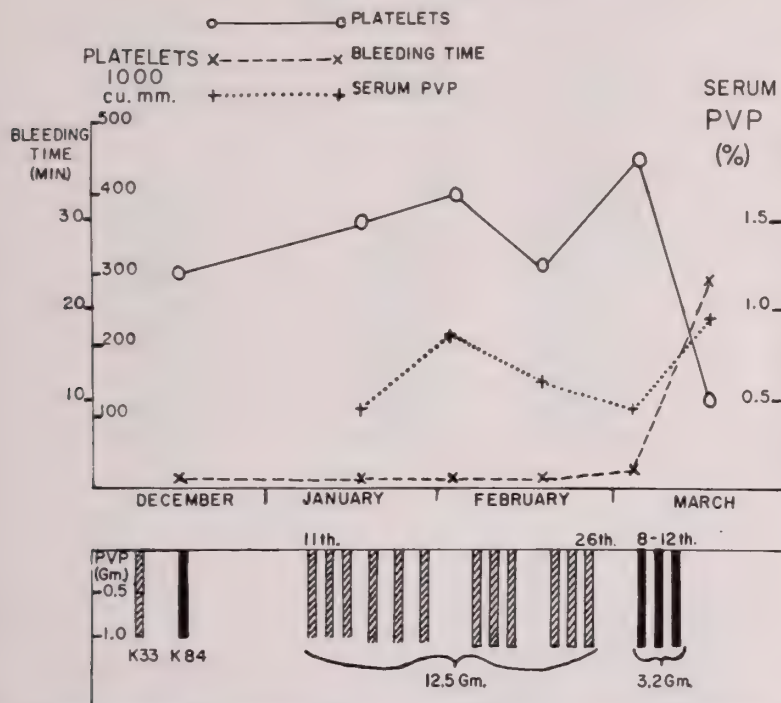


FIG. 1. Development of hemostatic defect after PVP administration. From the Department of Pathology, Mount Sinai Hospital, Chicago, Illinois.

preparation, since in rabbits first injected with K 33, smaller quantities of K 84, ranging from 3 to 4.5 Gm. were capable of bringing about abnormal findings. On the other hand, after K 84 had been given and abnormal values induced by it had returned to normal, relatively small amounts of K 33 were able to reduce platelet counts and prolong bleeding time; this was seen in rabbit # 128.

The sequence of events which occurred in rabbit # 130 is charted in detail in Figure 1.

- (1) 12.5 Gm. K 33 failed to affect hemostasis significantly;
- (2) additional 3.2 Gm. of K 84 brought about a precipitous drop of platelets and marked prolongation of bleeding time;
- (3) serum levels of PVP, after one-half of the total amount of K 33 was given, revealed a concentration of 0.73 per cent which was not associated with abnormal values of platelets or bleeding time, whereas a level of 0.97 per cent at the end of the experiment was accompanied by marked thrombocytopenia and prolongation of bleeding time.

It was not possible to correlate changes in hemostasis with concentration of PVP in the serum, determined according to the iodometric method by Cannan (4). Values ranged from 0.3 to 1.5 per cent, but similar concentrations were found before and after hemostatic abnormalities appeared and after they disappeared.

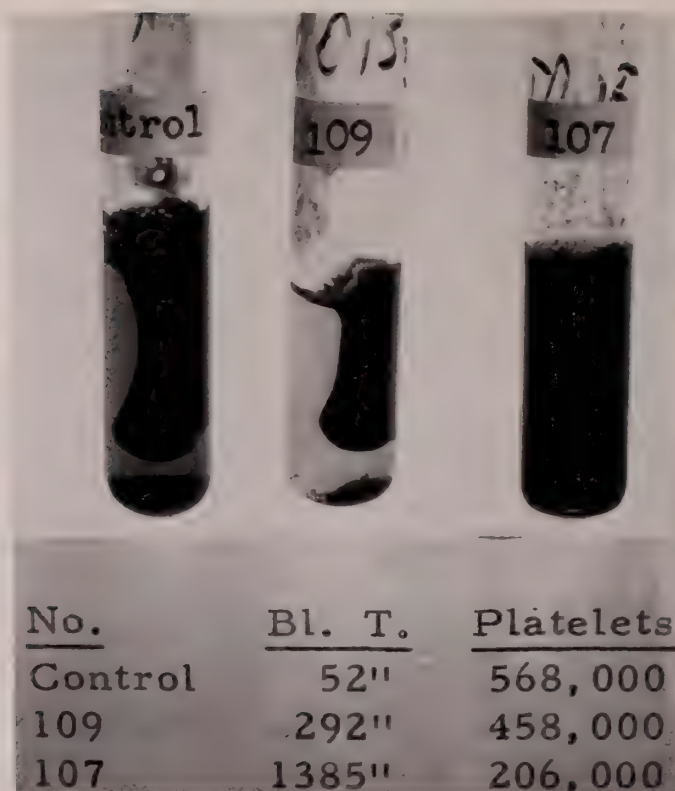


FIG. 2. Clot retraction in PVP treated rabbits.

Clot Retraction. In all instances where clot retraction was tested, thrombocytopenia was accompanied by delayed, deficient or absent clot retraction. On the other hand, specimens obtained from rabbits with moderately prolonged bleeding time associated with platelet values in the normal range showed normal clot retraction. This situation is illustrated in figure 2, depicting clot retraction in blood specimens 12 hours after withdrawal from a normal control, and from two PVP-treated rabbits. Of the latter, #107 with a platelet count of 206,000 showed no retraction at all, whereas complete retraction was observed in #109 with a platelet count of 458,000, although the bleeding time was still prolonged. In other instances delayed or deficient clot retraction occurred in blood specimens taken at a time when platelet values had already risen from abnormally low values; hence the abnormality in clot retraction may have resulted from qualitative defects in the platelets.

Reversibility of hemostatic disturbance

In all but a few instances to be mentioned later, the bleeding time and platelet count returned to normal within one to three weeks after abnormal findings were first noted. Spontaneous purpuric manifestations in living animals and in autopsies were rare.

In a few instances the change was of transient nature. It was demonstrated only a few hours after the last injection of PVP, and disappeared a few days later. On the other hand, in some instances a delayed appearance of abnormal hemostasis following the last injection of PVP was observed. For instance, in animals # 127 and 128, one week after the last injection of K 84 no abnormalities were found, but were present approximately two weeks later. Of a total of 16 previously not splenectomized rabbits, only one failed to show changes in bleeding time and platelet count after administration of PVP in amounts comparable to those given to the other rabbits. Apparently individual host factors are responsible for variations in the behavior of different animals, including the amount of PVP required for interfering with hemostasis.

Effect of Splenectomy

Two animals were subjected to splenectomy before administration of PVP. Findings are shown in Table II. Thrombocytosis developed in both after splenectomy. Rabbit # 108 showed a severe effect of administration of relatively small amounts, 4.4 Gm. of K 84, given within 8 days. One day later, the bleeding time rose to almost 20 minutes and the platelet count dropped from a postsplenectomy level of close to 700,000 to 210,000. Similarly, in rabbit # 107 which after splenectomy showed a rise of platelets to 800,000 and unchanged bleeding time, administration of only 2.6 Gm. of K 84 caused prolongation of bleeding time to 13 minutes, and drop of platelets to 162,000. Without further injection of PVP, the bleeding time rose a week later to 46 minutes, and dropped 10 days later to less than 5 minutes. The platelets remained at approximately the same low level.

Lethal dose of PVP. In three rabbits, administration of PVP was progressively increased until the animals began to show signs of ill health manifested by labored breathing, refused to eat, and died in 7 to 9 days. Up to 5 subcutaneous or intraperitoneal injections of a 10 per cent PVP solution (K 84) were given daily. As seen in Table III, rabbits # 111 (previously untreated) and # 109 (splenectomized previously) died after approximately 25 Gm. of PVP given

TABLE II
Effect of PVP on splenectomized rabbits

Rabbit No.	Date of Splenectomy	Period of Administration	PVP (Gm.) K 84	Date of Test	Platelets (10^3 per cu. mm.)	Bleeding Time (secs.)	Serum PVP (%)
108	2/25/54			2/24/54	400	55	—
				3/5	690	30	—
		3/15-3/17	2.6	3/18	350	124	1.28
		3/22-3/23	1.8	3/23	210	1170	1.42
107	2/25/54	3/15-3/17	2.6	2/24/54	470	35	—
				3/5	700	56	—
				3/18	162	795	1.19
				3/23	220	2760	1.34
				3/25	220	267	—

TABLE III
Lethal doses of PVP

Administration of PVP (K 84)				Date of Tests	Platelets (10 ³ per cu. mm.)	Bleeding Time (secs.)	Serum PVP (%)	Date of Death	Remarks
Rabbit No.	Periods	No. of Inj.	Total (Gm.)						
111	4/5-4/12	14	26.9	3/23	380	96	1.10	4/12	Intact animal
				4/8	440	480			
				4/12	54	420			
109	4/5-4/12	13	25.7	3/23	550	154	1.52	4/12	Splenec-tomized 3/25
				4/8	460	292			
				4/12	66	1235			
107	(a) 3/15-3/23	6	4.4	2/24	470	35	1.07		Splenec-tomized 3/2
				3/5	605	56			
				3/18	162	795			
				3/23	220	2763			
	(b) 4/5-4/12	14	28.1	4/8	206	1385	2.31		
				4/12	200	675	2.67		
				4/26	68	505	2.15		
	(c) 5/3-5/12	13	39.0	5/10	82	1200		5/14	

during one week. Rabbit #107 survived an even slightly larger dose of PVP given during one week, but succumbed to a course of PVP injections totaling 39 Gm. given during 9 days. During the periods of PVP administration, severe thrombocytopenia, delayed or absent clot reaction, and extreme prolongation of bleeding time were seen in all rabbits.

Gross Pathologic Findings

Autopsies were performed on the rabbits treated with lethal doses of PVP as well as on rabbits shown in Table I. The latter were sacrificed during different stages of the experiment, some animals after the abnormal findings had returned to normal, others while they were at their peak. Gross autopsy findings summarized in Table IV, showed no essential changes except for some degree of splenomegaly in animals injected with large amounts of PVP. In some also the adrenals were enlarged to about 2 to 3 times the normal size.

Rabbit #104 which had received approximately 23 Gm. of PVP, and exhibited a prolongation of bleeding time up to 24 minutes persisting for over three weeks and which appeared sick at that time, at autopsy showed purpura of the gastric mucosa (Figure 3) which might have been responsible for the illness of the animal. This was one of the few examples of spontaneous hemorrhage, probably resulting from endothelial damage, in animals treated with moderate amounts of PVP.

Severe gastrointestinal hemorrhages were noted in rabbits #107 and 109 which had been exposed to lethal doses of PVP. Rabbit #107 showed in addition

TABLE IV
Gross autopsy findings

Rabbit No.	Date	Body Wt. kg	Liver		Spleen*		Adrenals† (Gm.)	Kidneys	PVP %‡		
			Gm	% of Body Wt.	Gm	% of Body Wt.			Liver	Spleen	Kidney
101	3/22/54	3.6	113.5	3.2	3.0†	0.08	1.2	20.2	0.20	0.43	0.24
102	12/30/53	2.8	72.5	2.6	1.5	0.05	"enlarged"		0.30	0.32	—
126	1/21/54	4.5	116	2.6	5.5	0.12		—	0.09	0.28	—
128	1/21/54	4.2	136	3.2	3.0	0.07			0.04	0.54	—
130	3/17/54	3.1	114.5	3.3	3.5	0.11	0.7	28.0	0.31	0.59	0.23
106	3/17/54	3.8	136.5	3.6	8.5	0.22	1.3	22.3	0.34	0.75	0.34
104	3/30/54	4.6	131.5	2.9	4.0	0.09	0.9	21.5	0.33	0.56	0.17
105	3/30/54	4.8	131	2.7	3.3	0.07	0.9	19.8	0.28	0.96	0.34
129	3/30/54	4.2	122	2.9	2.5	0.05	1.4	20.2	0.35	0.77	0.30
108	3/23/54	2.7	123	4.6	1.9‡	0.08*	0.4	24.8	0.15	—	0.22
107	5/14/54	3.1	127	4.1	1.2§	0.05*	1.9	33.7	0.36	—	1.84
111	4/12/54	2.8	110	5.2	0.8	0.03	0.7	23.5	0.52	0.60	0.51
109	4/12/54	2.5	73	2.9	1.3	0.04*	1.4	23.0	0.31	—	0.40

* Normal range: 0.5–0.8 Gm./Kg. (5)

† Normal range: 0.1–0.2 Gm./Kg. (6)

‡ Splenectomy 1/14/54

§ Splenectomy 2/25/54

|| Splenectomy 3/25/54

• Calculated from body weight at time of splenectomy

pulmonary, perirenal and subcutaneous hemorrhages. Peritoneal and pleural transudates and subcutaneous and serotal edema were present in rabbits #109, 107, and 111.

Histologic findings

Microscopic studies revealed changes in accord with data in the literature on storage of PVP in reticulo-endothelial tissues. In addition to hematoxylin-eosin stain which was used routinely, some of the PVP containing tissues were also stained with iodine (7) or Congo red (8). The earliest deposition and the most extensive storage were present in the spleen (Figure 4). On the other hand, the liver showed less storage in early stages. Extensive deposits of PVP in Kupffer cells were found only after at least 4 weeks had elapsed between administration of PVP and death of the animal (Figure 5). Deposits of PVP were also found in septal walls in the lungs, in perivascular histiocytes in adrenals, and in reticulo-endothelial cells of bone marrow. Subcutaneous tissue and other areas of fat and connective tissue showed small deposits of PVP, e.g., in the connective tissue of the tunica albuginea of the testis. Larger deposits persisting for a long time evoked inflammatory reactions resulting in granuloma-like lesions which were most conspicuous in the spleen and liver. In the kidneys, vacuolation of tubular epithelial cells was interpreted as evidence of renal excretion of PVP (Figure 6).

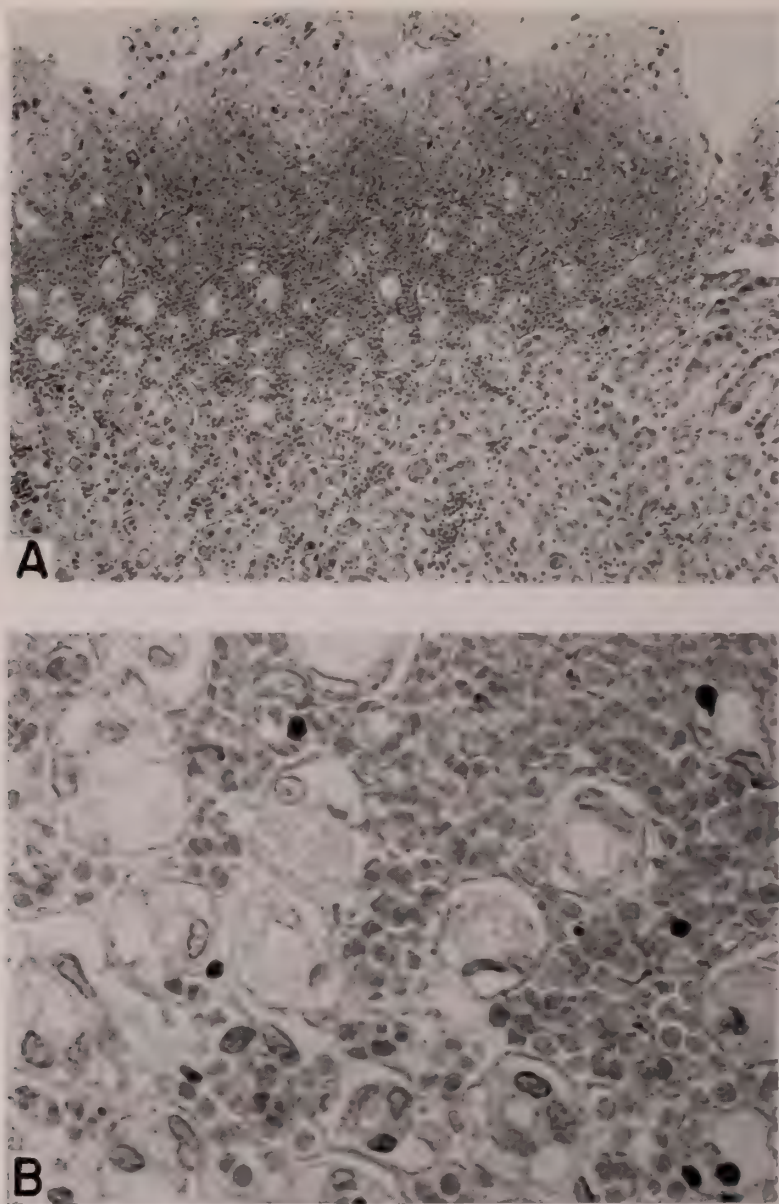


FIG. 3. Gastric mucosa. A. $\times 180$. Hemorrhage in superficial layer of gastric mucosa. B. $\times 760$. Details of changes in the deeper layer of hemorrhage showing PVP storage in individual reticulo-endothelial cells.

Bone Marrow

On comparing autopsy findings in rabbits sacrificed at the height of abnormal bleeding time and platelet counts, as well as those which had already recovered, it was possible to correlate the microscopic changes in the bone marrow with disturbed hemostasis. The other gross and microscopic changes showed no such

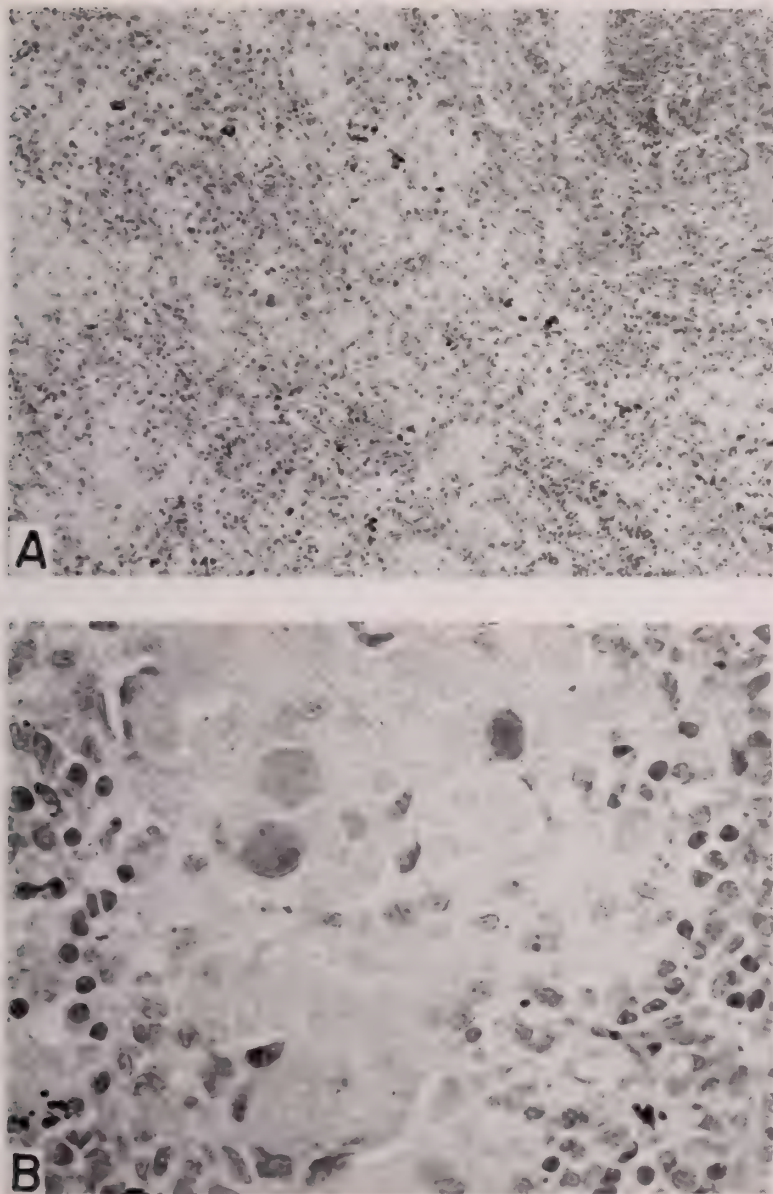


FIG. 4. Spleen. A. $\times 200$. Massive storage of PVP in reticulo-endothelial cells resulting in obliteration of follicles and pulp. B. $\times 650$. High power magnification showing storage and in left lower corner a granuloma with giant cell.

correlation. The characteristic findings in the bone marrow concerned the megakaryocytes. In animals with hemostatic abnormalities the nuclei of the megakaryocytes were pyknotic and did not reveal the fine chromatin and details of nuclear structure present in normal megakaryocytes. The cells appeared shrunken, and the fine cytoplasmic granularity of normal megakaryocytes was

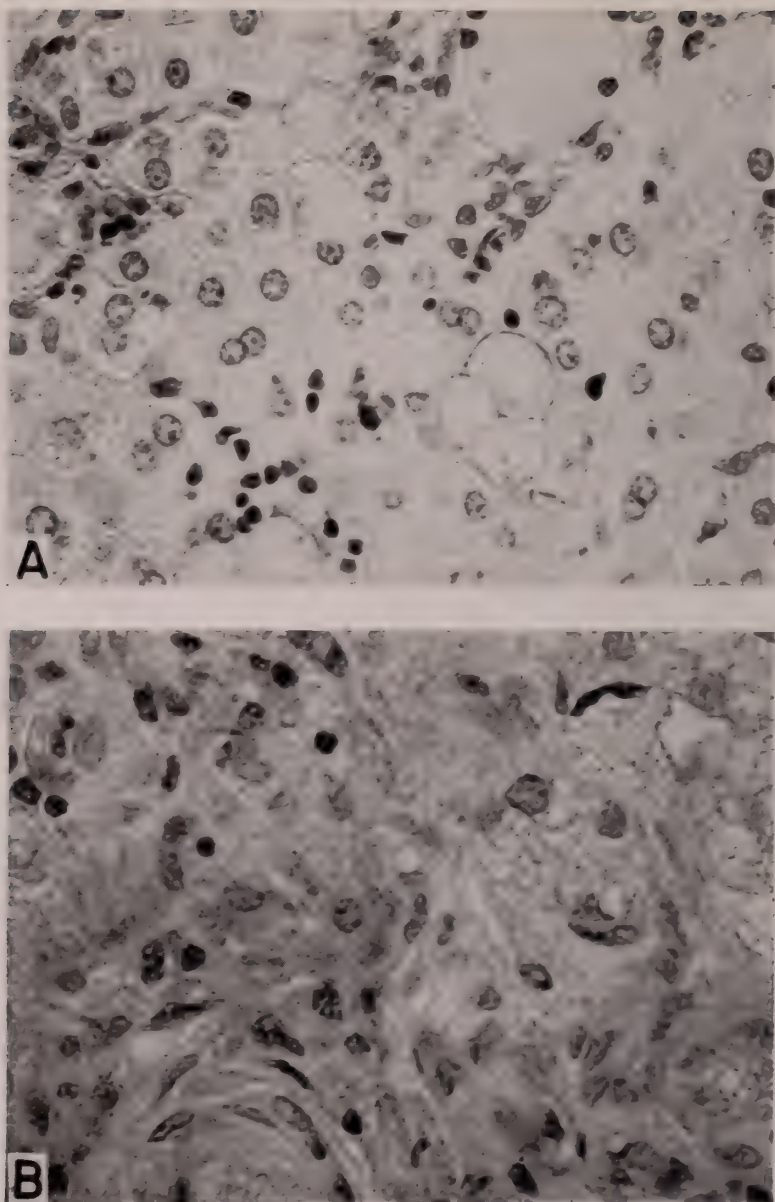


FIG. 5. Liver. A. $\times 650$. Storage of PVP in reticulo-endothelial cells. Note large foam cells. B. $\times 850$. Granuloma in left lower corner and many foam cells in other areas.

absent (Figure 7). Transitions from less to more advanced degenerative changes were observed. In some animals such abnormal megakaryocytes represented the majority, whereas in others both normal and abnormal, degenerated, megakaryocytes were present. Although the material is not large enough it is suggestive of a positive correlation of the number of degenerated megakaryocytes with the

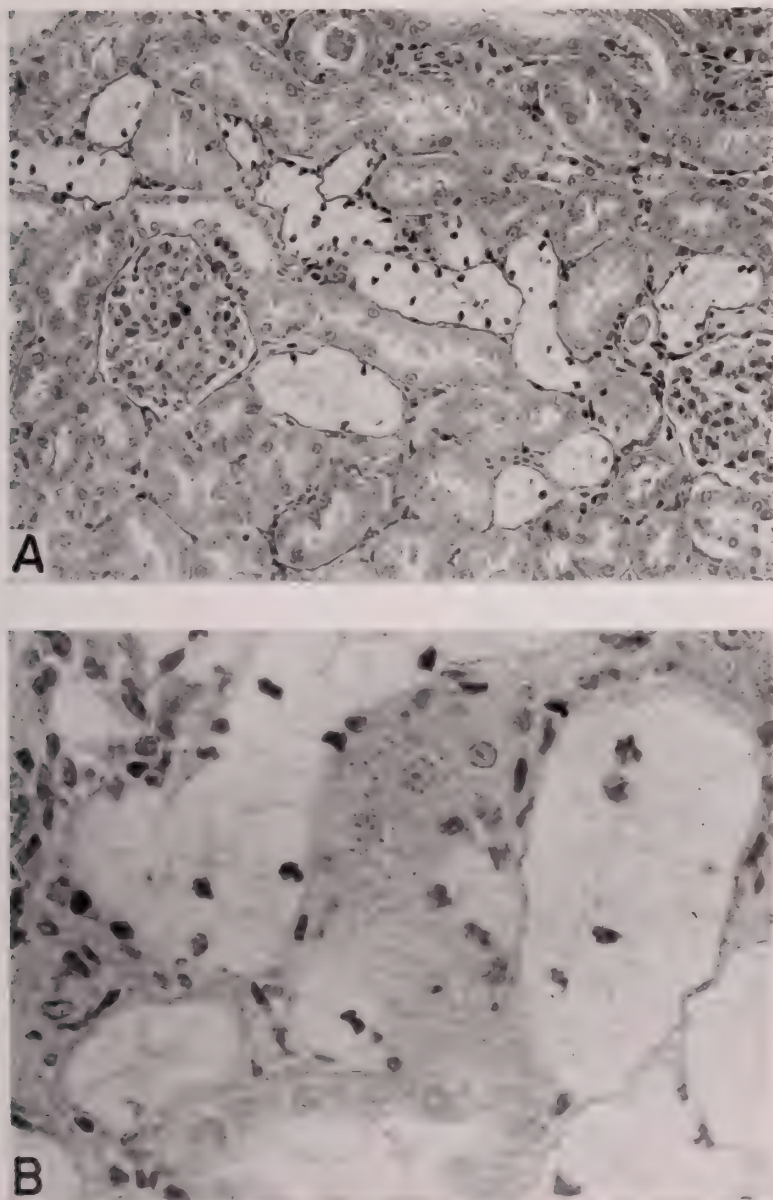


FIG. 6. Kidney. A. $\times 260$. Storage of PVP in tubular epithelial cells indicative of excretion of PVP. B. $\times 650$. Higher magnification of A.

reduction of platelet count and prolongation of bleeding time. In rabbits treated with lethal doses of PVP, there was also a reduction in the total number of megakaryocytes and the bone marrow appeared hypocellular with focal areas of hemorrhage. In a few rabbits autopsied at the peak of the hemostatic disturbance, megakaryocytes were found in the lung and spleen.

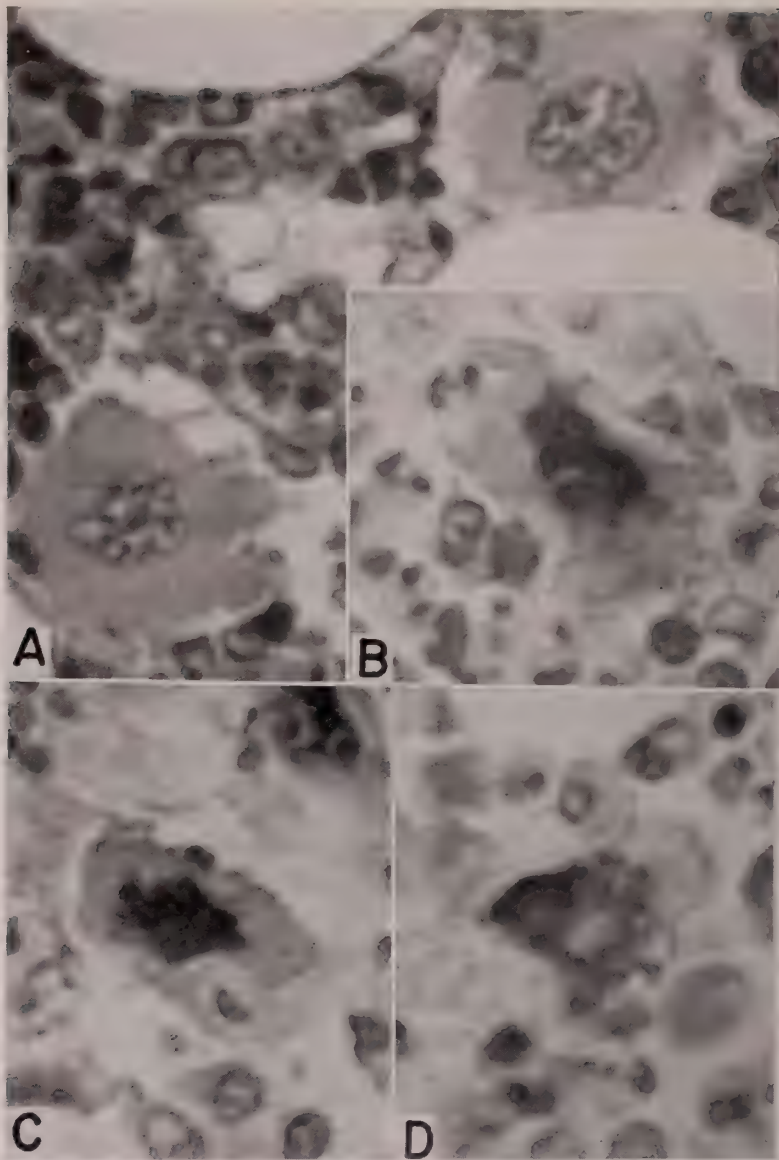


FIG. 7. Bone Marrow. A. $\times 1600$. Bone marrow of control rabbit with two normal-megakaryocytes. B. $\times 1600$. Rabbit #106. Megakaryocyte showing moderate degenerative changes, but lobes of nucleus still discernible, outlines of cytoplasm fairly well preserved. C. $\times 1500$. Rabbit #130. Two megakaryocytes showing more advanced changes with obliteration of nuclear structure and of cytoplasmic detail. D. $\times 1600$. Rabbit #106. Farther advanced degenerative change with almost complete loss of identity of megakaryocyte and obliteration of nuclear and cytoplasmic details.

DISCUSSION

Several explanations might be considered in an attempt to account for the disturbance in the hemostatic mechanism brought about by PVP. Administration of finely dispersed colloid matter such as suspensions of silica (9) or of india

ink (10) can bring about transient reductions of the platelet count in the rabbit, reverting to normal within 24 hours. No mention was made of prolongation of bleeding time. The size of the PVP molecule cannot be compared with that of finely dispersed particles such as india ink. Nevertheless, K 84 with larger molecular size was more effective than K 33.

The summary report on blood substitutes made available by the U. S. Department of Commerce (11) contains data compiled from the original German sources on properties of PVP. Experiments are quoted according to which bleeding time of dogs was not affected 24 hours after infusion of PVP, and negative Rumple-Leeds test, and normal bleeding and coagulation times were obtained in patients treated with PVP. In contrast, administration of gum arabic led to a prolongation of bleeding and coagulation time. This is reminiscent of the "hematologic macromolecular syndrome" described by Hueper (12) consisting of a transient leukopenia, thrombocytopenia, anemia and prolonged coagulation time in dogs, rabbits and rats shortly after injection of various nonphysiologic macromolecular solutions.

Another compound of macromolecular type and proposed for use as plasma expander, namely dextran, has been implicated in a disturbance of the hemostatic mechanism (13). Human volunteers showed prolongation of bleeding time and reduced prothrombin activity.

Palmer and associates (14) produced in rats massive splenomegaly, anemia, leukopenia, and mild thrombocytopenia by intraperitoneal injections of methyl cellulose. Since these changes did not occur in previously splenectomized animals the authors suggested the possibility of interpreting the syndrome as the expression of experimental hypersplenism. This mechanism does not seem to be applicable to the effect of PVP observed by us since (a) it occurred more readily in splenectomized than in intact rabbits; and (b) thrombocytopenia was much more severe in our experiments and was not accompanied by anemia and leukopenia.

Baillif (15) studied the effect of colloidal thorium in the rat. He noted in splenic megakaryocytes a shrinkage of the nucleus, irregularity of nuclear chromatin pattern and pyknosis. No hemostatic deviations were recorded.

We would like to propose the hypothesis that four factors may be involved in disturbances of the hemostatic mechanism in PVP-treated rabbits: (a) Damage to the endothelial lining of the blood vessels. This appears to be a reasonable assumption in view of the reticulo-endothelial storage of the compound and its ultimate perivascular location in some organs. The disturbance of the endothelial integrity could explain the prolonged bleeding time which seems to be the first abnormal finding in the rabbit. This change in turn might be responsible for a greater consumption of platelets in the circulation. (b) Degeneration of megakaryocytes in the marrow. The change could be caused by a direct damage of PVP to the megakaryocytes, or it could be the expression of a degeneration of "overwork" exhibited by megakaryocytes which are called upon to replace platelets beyond normal demands. (c) Allergic mechanisms have been found responsible for thrombocytopenia in man. Experimentally induced hypersensitivity can produce thrombocytopenia in animals. (d) PVP has been found

capable of causing platelet agglutination (16), and in this way may mechanically remove platelets from the circulation.

No decision as to which one of these possibilities actually prevails can be made at this time. It may be that any one, any combination of two or all four may be involved.

Gall and associates (17) found that storage of PVP in human liver was observed regularly 6 months after the compound was injected, but was absent, or rarely present, up to 3 months after administration. This is in accord with our findings in rabbits where the liver showed storage only after prolonged time whereas in earlier stages the spleen contained the bulk of the material.

Since our first report (3) on the derangement of hemostasis brought about in rabbits by PVP, other authors have obtained results that in general are in good accord with our observations. Karp and Bloom (18) carried out short term experiments on rabbits injected with large amounts of PVP or dextran. Prolongation of bleeding time resulted from this treatment, and the lethal dose of PVP averaged 15.8 Gm/kg., a value in the same range as in our more chronic experiments (cf. Table III). In their extensive studies on plasma expanders, Behrmann and Hartman (19, 20) observed changes in dogs injected with dextran or PVP: decrease in platelets, fibrinogen and prothrombin occurred within four hours and prolonged bleeding time and delayed clot retraction were also noted (19). They suggested that these effects were the result of intravascular agglutination of platelets with subsequent removal of the agglutinates by spleen and other reticulo-endothelial tissues; they postulated that the hypofibrinogenemia may be caused by formation of complexes between fibrinogen and the macromolecular compounds as well as by liver damage. Confirmation of the role of the spleen in the thrombocytopenia was seen in the fact that splenectomized dogs treated with PVP or dextran showed lesser degrees of thrombocytopenia. Degenerative changes in the megakaryocytes of the bone marrow were also noted by the authors in dogs after repeated injections of dextran or PVP (20). Thus, some of their findings are similar to those reported by us in 1954, while other data, e.g., the partial protection of splenectomized dogs against thrombocytopenia contrasts with our observation that splenectomized rabbits developed thrombocytopenia and prolonged bleeding time more rapidly than did intact rabbits (cf. Table II). These discrepancies may well reflect differences in biologic responses of these two species, viz., dogs and rabbits, as well as differences in the experimental procedures used.

Certain species differences seem to exist in storage as well as possibly in effects of PVP. In the mouse we have noted previously (1, 2) that storage affects liver and spleen about equally, possibly with some preponderance of the storage in liver. In the rabbit, on the other hand, the spleen appears to be the first station of storage. This probably explains the fact that after splenectomy rabbits showed the disturbance of the hemostatic mechanism earlier than intact animals.

In experimental work where PVP was given to mice and rats for long periods, we have not noted any obvious disturbance of the hemostatic mechanism. Unpublished preliminary observations suggested that the bleeding time is prolonged in rats and mice after they had been injected with PVP for several months.

Finally, a word of caution may be added regarding the application of our observations in man. So far there is no evidence that PVP can bring about changes in man similar to those found by us in rabbits. Furthermore, it must be kept in mind that PVP as well as other so-called plasma expanders may have entirely different effects depending on whether the compound is administered to normovolemic or hypovolemic hosts. In our experiments, rabbits with normal blood volume were injected with the compound; it is possible that phenomena of storage as well as interference with other bodily functions may be facilitated under these conditions, as compared with administration of PVP to hosts with severely reduced blood volume, in which the compound may remain in the intravascular compartment for a longer time.

SUMMARY

1. After administration of sufficient amounts of PVP of suitable molecular size, almost all rabbits so treated showed prolonged bleeding time and reduced platelet counts. The latter was accompanied by absent or deficient clot retraction.
2. These changes were found to be reversible in most instances. Minimal lethal doses of PVP in the rabbit ranged from 10 to 25 Gm. per kg. of body weight.
3. Autopsy findings disclosed, in addition to the expected storage and some granulomatous reaction to PVP, degenerative changes in the megakaryocytes in the bone marrow.
4. Some factors that might be responsible for these effects of PVP were discussed.
5. Reference was made to work by other authors who studied hemostasis in animals treated with macromolecular compounds, and the possibility of species differences in biologic effects of PVP was considered.

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MYELOLIPOMA OF THE ADRENAL WITH CLINICAL FEATURES AND SURGICAL EXCISION

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Myelolipoma of the adrenal is a relatively rare tumor composed of hematopoietic and fatty tissue. Previous reports have all indicated that these lesions were incidental findings at autopsy. Such tumors have invariably been too small to produce sufficient clinical symptoms or signs which would make possible their discovery during life. The present report deals with the largest myelolipoma of the adrenal to be recorded and the first such case to produce clinical findings leading to surgical excision of the tumor.

CASE REPORT

A 47 year old white male (M. S.) upholsterer was hospitalized because of abdominal pain in the right upper quadrant radiating to his back of five days duration. The pain was quite sudden in onset and apparently not preceded by trauma. However, three weeks before onset of his pain he lifted a sofa and found he could not straighten up for about 15 minutes. Past history was non-contributory. There was no history of renal disease, malignancy or advanced atherosclerosis as has been described in other cases of myelolipoma. Physical examination revealed a blood pressure of 116/94 and temperature of 100.8°F. There was some tenderness and slight rigidity in the right upper quadrant of the abdomen. There was also some tenderness in the right costovertebral angle. Physical examination otherwise was negative. Urinalysis was normal. Blood counts showed a mild anemia with hemoglobin 11.2 grams per cent and red blood cell count 3,650,000 per cu. mm. The white blood cell count and differential were normal. Blood sugar, urea nitrogen, total protein and albumin globulin ratio, thymol turbidity, cephalin flocculation and prothrombin time were all normal. The icterus index was slightly elevated (12.8 units). An extensive x-ray work up including a gall bladder series, gastro-intestinal series, barium enema, intravenous pyelogram, retrograde pyelogram with tomographic studies and retroperitoneal studies were all done. The gall bladder was found displaced toward the midline. The anterior end of the stomach, the duodenal bulb and the loop in its first portion were displaced anteriorly. The right kidney was displaced inferiorly and anteriorly. A definite rounded low density immobile soft tissue mass with a well delineated lower border and thought to be largely fat tissue was noted in the right upper quadrant. Tomography of this mass did not delineate any definite cleavage planes. Retroperitoneal air studies showed

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the right kidney to be distinct from the right upper quadrant mass. The psoas shadows were visualized.

At operation the tenth and eleventh ribs were resected and the retroperitoneal area exposed. A large tumor mass which was depressing the right kidney and estimated about six inches in diameter was removed by careful blunt dissection. The tumor was found to fuse with the adrenal gland so that the latter had to be removed in part and the remainder sutured with gelfoam to control hemostasis. During excision of the mass the pleural cavity was entered and the diaphragm sutured with a catheter in place in the lower angle of the pleural cavity. Post operatively there was some segmental atelectasis at the right base. The patient, however, made an uneventful recovery and was discharged on the ninth post-operative day. Two years of follow-up have revealed no significant changes although there has recently been some complaints of left upper quadrant pain which after x-ray studies were attributed to diverticulitis.

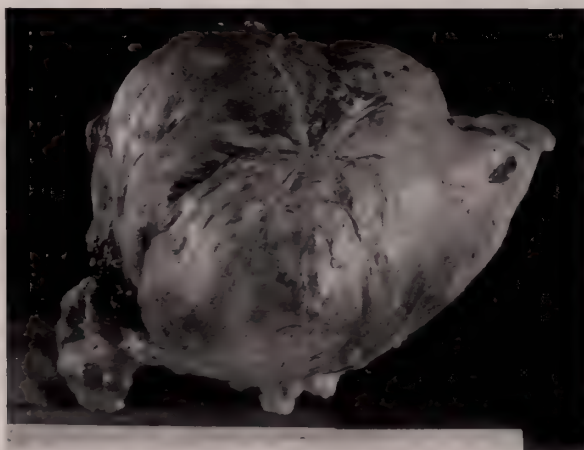


FIG. 1. Myelolipoma of adrenal showing external surface.

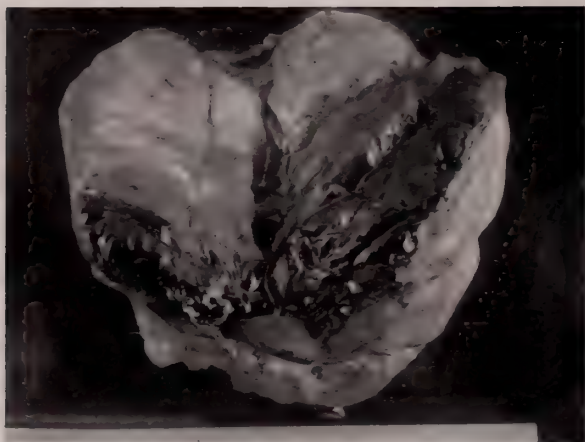


FIG. 2. Myelolipoma of adrenal, sectioned. Note hematoma.

SURGICAL SPECIMEN

The tumor was a large fairly well encapsulated soft mass which measured 16 x 13 centimeters in its diameters and weighed 1100 grams (Fig. 1). The capsular surface showed irregular patchy areas of yellow-orange, red and yellow. Some areas were bluish-red suggestive of an underlying hematoma. Multiple sections showed a predominantly yellow, soft, fatty tumor with irregular angulated patches of dense yellowish-grey, brown and dark red corresponding to areas of fat necrosis and hemorrhage (Fig. 2). An estimated one sixth of the tumor was occupied by a large bluish-red hematoma. There was an occasional narrow scarred area which usually seemed to separate necrotic and viable appearing fat tissue. There were no areas of calcification. Separately received were two segments of ribs which showed no significant changes.

Microscopically, the yellow-orange portion of the outer shell of the tumor

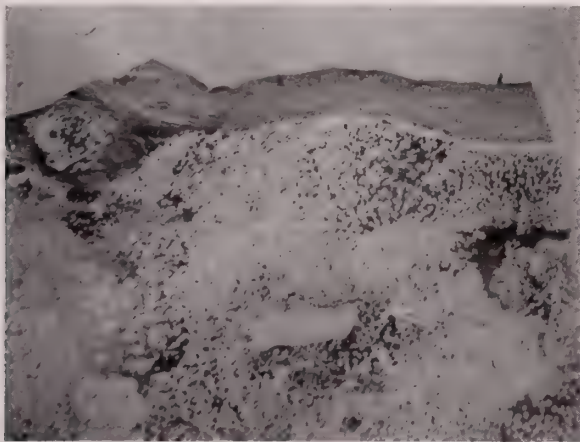


FIG. 3. Myelolipoma of adrenal. Low power view showing surface layer of adrenal tissue and deeper fibrous and adipose tissue with areas of hematopoiesis. At lower left is a large area of fat necrosis.

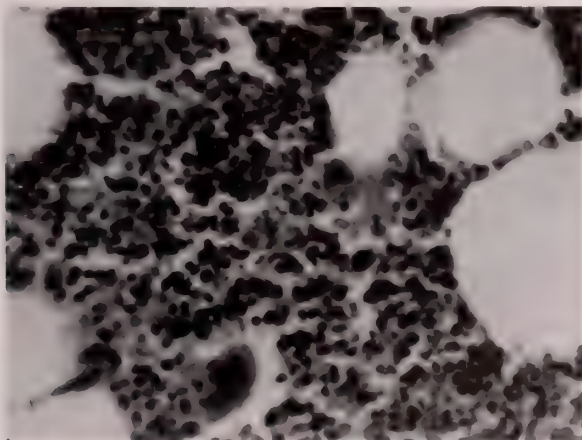


FIG. 4. High power view of hematopoietic area within the tumor.

showed adrenal cortical tissue. Underlying this was a layer of fibrous tissue of variable thickness and deeper portions of fatty tissue with foci of hematopoiesis (Figs. 3 and 4). The fatty tissue which was by far the largest component of the tumor showed large areas of necrosis with bordering lipophagic reaction, interstitial hemorrhage and hemosiderin deposits. Selected sections showed some bands of scarring. The hematopoietic tissue was found more often near the surface of the tumor. It showed erythropoietic and myeloid elements along with megakaryocytes in what appeared to be a normal ratio. Except for an increased amount of hemosiderin pigment in the tumor, the hematopoietic tissue was indistinguishable from that in the sections of rib taken from the same patient.

DISCUSSION

The clinical features of this unusually large myelolipoma of the adrenal are, of course, mainly related to its size and position. The areas of fat necrosis, hemorrhage and hemosiderin deposits are conceivably the result of trauma to the tumor. It is probable that the rapid increase in size of the tumor resulting from the hemorrhage gave rise to the patient's pain and the resorption of hemoglobin pigments to his elevated icterus index.

The roentgenologic features are significant in that they may make possible a correct presumptive diagnosis before operation. The findings are those of a low density tumor mass having the radiotranslucency of fat tissue and localized to the adrenal area.

From the pathologic point of view, aside from the tremendous size of the tumor, an unusual feature is the extent of fat necrosis and hemorrhage. While no calcified areas were observed in this tumor, it is not unlikely that with time such areas of fat necrosis may become calcified and eventually also ossified.

Collins (1) and Giffen (2) summarized the literature on myelolipoma and various theories concerning its histogenesis. Additional case reports (3-6) have since appeared some with comments on the mode of origin of this tumor. The present case report offers no new concept concerning the origin of myelolipoma, but because of its unusually large size emphasizes its neoplastic nature.

SUMMARY

A case of myelolipoma of the adrenal is reported. The tumor is the largest heretofore recorded and the first to give rise to clinical features leading to its excision.

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OBSERVATIONS ON CONNECTIVE TISSUE ALTERATIONS IN COLLAGEN DISEASES

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The man whom we wish to honor by this Festschrift is known best for the creation of a new concept. By a process of observing, searching and thinking rather than by doing, he came to recognize that a certain group of maladies which had long resisted comprehension was characterized primarily by systemic alteration of the connective tissue. The concept of collagen or connective tissue diseases which sprang from this recognition has stimulated a large volume of research. As a result of these studies our knowledge of these diseases and of the connective tissue has been vastly expanded.

Since Klemperer and his associates introduced the new concept fifteen years have gone by (1). It may be in order, therefore, to reexamine some of the foundations on which it was built. As Klemperer in his Harvey lecture (2) indicated that it seemed advisable to him "to defer a search for cause and to concentrate upon an exploration of the nature of the abnormal component and its origin" (pg. 111), the present examination will be limited to a discussion of the nature of mucoid degeneration, serous inflammation, and fibrinoid degeneration.

MUCOID DEGENERATION AND SEROUS INFLAMMATION

Mucoid degeneration of connective tissue is characterized by intercellular accumulation of acid mucopolysaccharides, notably hyaluronic acid. In a lecture delivered at the University of Oxford, Cameron and Abraham (3) have appropriately summarized our knowledge of this degeneration by saying that "the whole business of mucus formation and the chemistry of mucopolysaccharides is still in a state of flux, and pathologists must wait until these matters are settled before they can put their own house in order."

Serous inflammation has gained much in attention since it was restudied by Roessle (4) some 20 years ago. It resembles other forms of inflammation in that it begins with "dysoria" (5), that is, increased leakage of water, proteins and other components of the plasma into the connective tissue. It differs from edema in that the "exudate" is rich in proteins, and that the enzymes (or enzyme activators) which escape with the proteins tend to cause lysis of the ground substance and fibers. Roessle (4) spoke of "desmolysis" or "histolysis". Studies of the synovial fluid in rheumatic fever, rheumatoid arthritis and lupus erythematosus disseminatus by Bauer and associates (6) indicate that polymorphonuclear leukocytes and macrophages though not numerous in serous inflammation may reach concentrations of 10,000 to 14,000 per cbmm of intercellular fluid. Fibrin, on the other hand, is not a significant feature of serous inflammation indicating

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that the dysoria, or the increase in permeability of the capillaries, is not of a magnitude which would permit particles of the size of fibrinogen molecules to pass readily through the filtering membrane.

It is believed by many that the initial lesion in the collagen diseases consists of an increase in ground substance, and that this mucoid degeneration is the same as serous inflammation (7, 8). If one looks at the ground substance under various pathological conditions, however, one cannot help but notice that in some cases of mucoid degeneration the increased ground substance contains poorly polymerized mucopolysaccharide-protein complexes and abundant water (also free water), while in other cases it appears to be highly polymerized and to contain comparatively little water (only bound water). The former is found in scurvy (9, 10). It is demonstrated readily as an initial or collateral phenomenon in various forms of inflammation (suppurative inflammation caused by turpentine (9), experimental arthritis (11), human gingivitis (12)). It is an outstanding feature of serous inflammation. Highly polymerized ground substances containing comparatively little (bound) water occurs in myxedema due to hypothyroidism (13) and in breasts stimulated by estrogen. It is the substance apparently of the common endocardial cushions described and illustrated so well by Böhmig and Klein (14). It may well be an initial alteration in scleroderma.

Chemical and physico-chemical studies of synovial fluid (ground substance) in collagen diseases (6, 15, 16, 17, 18, 19) indicate that the intercellular substance is markedly increased in serous inflammation, but that its hyaluronic acid concentration tends to be moderately, and its viscosity greatly reduced. These observations may be taken as evidence that both water and ground substance are markedly increased in mucoid degeneration in inflammation, that the water tends to be increased more than the ground substance, and that the latter is poorly polymerized, its molecular components being in a state of dispersion.

Chemical studies by Ludwig, Boas and Soffer (13) and others have shown that connective tissue in myxedema due to thyroidectomy and stimulation by TSH also contains an increased concentration of ground substance and water, but in this case the increase in mucopolysaccharide was ten times that of water, indicating that the ground substance was highly polymerized and only contained bound water.

These chemical and physicochemical observations are in accord with the results of functional studies. It was pointed out some 30 years ago by the eminent physicochemist Schade (20) that forces which induce dispersion of ground substance cause increased diffusibility. Zweifel (21, 22) has shown directly that graphite particles which normally are difficult to insert into ground substance spread readily to a distance of 100 mikra during early stages of inflammation. Evans-blue which normally diffuses slowly, spread rapidly to a distance of several hundred mikra. Also, it has been known since more than 80 years that the flow of lymph is accelerated in inflammation (23, 24). If Altshuler and Angevine (7, 8) contested Schade's observation by stressing the statement of Duran-Reynals (25) that inflammation may be accompanied by decreased spread, they failed to take into account the mechanism of fixation which was explored in detail by Menkin (26, 27). The latter appears to be a function of precipitated fibrin (15).

On the other hand, gelating forces which favor polymerization of ground substance cause decreased diffusibility as was pointed out by Schade (20). That this observation was correct, was shown by Seifter and associates (28) who demonstrated that synovia containing highly polymerized ground substance is much less permeable to PSP than normal synovia.

These various observations seem to show that mucoid degeneration occurs in two forms. One is characterized by poor polymerization of the ground substance, abundant (also free) water and a high degree of diffusibility, the other by high polymerization, comparatively little (only bound) water and little diffusibility. Only the former is a feature of serous inflammation. The outcome of the two forms of mucoid degeneration, however, seems to be the same, for it is well known that both may terminate in sclerosis.

FIBRINOID DEGENERATION

If an inflammation is such that capillary permeability is increased to permit the escape of significant amounts of globulin and fibrinogen into the connective tissue, a network of fibrin may form. We then speak of fibrinous inflammation. Like serous inflammation, this is associated with desmolysis or histolysis (29). But unlike serous inflammation it tends to cause "fixation", that is, retention on the field of inflammation of particles, colloids and even solutes (26, 27). The latter is due apparently to adsorption by the fibrin network (15).

From fibrinous inflammation fibrinoid degeneration has been distinguished since first described by Neumann some 80 years ago (30). Our present knowledge of this alteration has been ably reviewed recently by Klemperer's and the author's pupil and associate Wagner (31). While Klemperer, Pollack and Baehr (1) first agreed with Neumann (30) that fibrinoid represented a degenerative abnormality of the collagen fibers due to a defect in its protein moiety, and while Altshuler and Angevine (7) concluded that fibrinoid formation was primarily "the precipitation of the acid mucopolysaccharides of the ground substance", and that "the precipitant in some instances was probably an alkaline protein derived from necrosis of tissue or the interaction of tissue with a damaging agent", this author (32, 33), and Brunson and associates (34, 35), like Roessle's pupil W. Meyer (36, 29), stressed the presence of fibrinogen or fibrin in this material. According to W. Meyer (29) fibrinoid alteration begins with impregnation of connective tissue with serous fluid (serous inflammation). Then fibrin fibers and networks are formed and these undergo condensation to homogeneous fibrinoid precipitates in part as a result of the mechanical forces which prevail in the affected tissue. Meyer came to the conclusion that fibrinoid degeneration is a fibrinous inflammation whose peculiarity is its location within connective tissue. Hence he spoke of "interstitial fibrinous inflammation."

It is true that Altshuler and Angevine (7) have stated that fibrinoid does not necessarily contain fibrin. However, in experimental lipid nephrosis, where the genesis of this material could be studied from the beginning (33), the fibrinoid contained in the filtering membrane of the glomeruli was found always to stain like fibrin during the first three days of the experiment while thereafter silver fibrils made their appearance and the fibrinoid stained like collagen instead of

fibrin. Hence, it was concluded that the absence of a positive fibrin reaction cannot be taken as evidence that a given material is not a derivate of fibrin or fibrinogen.

That fibrin is indeed present invariably in fibrinoid was demonstrated recently by Gitlin, Craig and Janeway (37) through application of fluorescein-labelled rabbit antisera against human fibrin to sections of fibrinoid lesions from patients with rheumatic fever, rheumatoid arthritis, lupus erythematosus disseminatus, dermatomyositis and periarteritis. Also, it was shown that the conventional staining methods for fibrin do not necessarily reveal fibrin if present for they sometimes gave negative results in areas in which fibrin could be demonstrated by fluorescent antibodies. It is noteworthy that Gitlin and associates concluded that the finding of fibrin in fibrinoid does not preclude the presence of other substances. In fact, they expected that other plasma proteins, nucleoprotein and other materials "may increase in concentration in (these) areas of inflammation".

While Gitlin, Craig and Janeway's paper was still in press, Dixon (38) presented before the Pathological Society of Philadelphia his observation that the application of fluorescein-labelled antibody against human gammaglobulin shows also this plasma protein invariably present in Aschoff bodies, L. E. cells and the fibrinoid of various collagen diseases. He concluded that the gammaglobulin was the cause of the lesions, and as this was probably antibody, the presence of gammaglobulin was evidence that the collagen diseases were all allergic in nature. It was pointed out at a recent research conference on connective tissue diseases (39) by this writer, and by Good, that scleroderma, rheumatoid arthritis, lupus erythematosus disseminatus and dermatomyositis have now been observed in patients with congenital agammaglobulinemia. Hence, it was consented that the theory, proposed by this writer some years ago (32), that the collagen diseases are dysgammaglobulinemias, is no longer tenable. As patients with agammaglobulinemia cannot form precipitable serum antibodies, the spontaneous occurrence of the above collagen diseases in such patients would indicate that these four diseases are not allergies of the Arthus or anaphylactic type. The possibility of other allergies such as of the delayed or bacterial type, however, is not excluded by this observation.

Conventional histochemical analyses of fibrinoid in recent years have shown that fibrinoid may also contain nucleoprotein (in lupus erythematosus disseminatus) (40), derivatives of smooth muscle (in malignant arteriolar sclerosis), (41), and collagen (in rheumatic fever) (42, 31). Apparently, fibrinoid is not a uniform substance, but there are a variety of fibrinoids which have in common that they stain alike (31), and that they contain both plasma and tissue components. But while the tissue components vary considerably, gammaglobulin is usually, and fibrin always, present. This observation justifies the conclusion, accepted now also by Klemperer (40, 2), that fibrinoid originates primarily in the circulating plasma.

But while Klemperer (40, 2) still believes, it seems, that fibrinoid alteration is essentially a degenerative process although fibrinoid "when deposited in the vascular wall provokes a nonspecific inflammation which may simulate a necrotiz-

ing arteritis", the consistent presence of gammaglobulin and fibrin in fibrinoid indicates an increase in capillary permeability of a degree not seen in conditions other than inflammation (15). The fact that polymorphonuclear leukocytes or macrophages are usually not numerous in fibrinoid degeneration cannot be held against the inflammatory theory for this is true also for serous inflammation (see above). The comparative scarcity of leukocytes in fibrinoid inflammation may be due perhaps to disappearance of these cells before conglomeration and homogenization of fibrin takes place, or leukocytes may not be attracted because of lack of mediators necessary for their emigration.

However, if fibrinoid alteration is not a degeneration but an inflammation, our thoughts on its pathogenesis must be reoriented. Then the question is no longer how the fibrinoid components arrived in the connective tissue, but why the fibrin was conglomerated instead of resorbed. There can be little doubt that the resorption of fibrin is primarily a function of proteolytic enzymes, and that the leukocytes play an important role in this respect (15). It is possible therefore that the failure of resorption of this protein in fibrinoid inflammation is due to scarcity of leukocytes, or that it is caused by an unfavorable hydrogen ion concentration or some other condition which would interfere with proteolytic activity.

The fate of fibrinoid has been well studied by W. Meyer (36). He found that it is removed by a combination of humoral and cellular mechanisms. Formation of cavities in the hyaline material is associated with proliferation of connective tissue cells and new formation of fibers. Like mucoid degeneration and serous inflammation it terminates finally in sclerosis.

In summary we may say then that the consistent presence in fibrinoid of fibrin, and mostly also of gammaglobulin, is evidence that it originates at least in part in the circulating plasma, and as no significant amount of fibrinogen can escape into the connective tissue apparently in conditions other than inflammation, that fibrinoid alteration is not a primary degeneration of the connective tissue, but a form of fibrinous inflammation, whose peculiarity is condensation and homogenization of the exudate instead of its resorption by proteolysis.

We may conclude, therefore, that continued "exploration of the nature of the abnormal component and its origin" (2) has led to new interpretations of the foundations on which the concept of collagen diseases was built. However, the foundations themselves have not changed, which speaks well for the soundness of Klemperer's creation.

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METASTASIZING "ADENOMA" OF THE THYROID GLAND

A BRIEF RECONSIDERATION, WITH REPORT OF TWO CASES

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In 1926, C. Wegelin (1), in discussing the controversy which had been started fifty years earlier by J. Cohnheim (2) in a paper entitled "Einfacher Gallertkropf mit Metastasen" (simple colloid goiter with metastases) remarked that scarcely any neoplastic disease had been so hotly contested in the previous decade. If the temper of the literature on this subject since that time has abated somewhat, the issues raised remain as thought-provoking as ever. The challenge of the unsolved riddle of the production of metastases by a histologically benign tumor is not lightly to be set aside as growing out of inadequate study of the microscopic structure of the primary lesion in the thyroid gland. Reference has repeatedly been made by competent authorities to the encounter of metastatic nodules formed of tissue resembling normal thyroid parenchyma in association with a histologically benign lesion in the thyroid gland (1-5). This anatomical paradox occurs in a clinically distinctive form. Whereas so-called "lateral aberrant thyroid adenoma" tends to masquerade clinically as a primary disease of the lymph nodes of the neck, while the guilty primary tumor in the thyroid gland goes undetected for long periods of time, in metastasizing thyroid "adenoma", the clinical disguise is that of a primary neoplasm of bone. The metastasis grows very slowly, destroys bone, may be associated with pulsation and murmur, and often leads to spontaneous fracture. The following vignette by Masson (4) effectively summarizes the usual experience in this disease. "*Cette curieuse néoplasie se manifeste habituellement de la façon suivante. Une tumeur d'un os plat, la fracture spontanée d'un os long (surtout le fémur), sans consolidation ultérieure, conduisent au diagnostic clinique d'ostéosarcome. L'histologiste consulté reconnaît un Adénome thyroïdien qui peut être d'un typisme parfait. C'est alors que le chirurgien examine le corps thyroïde. Celui-ci est souvent nettement hypertrophié. Parfois il est cliniquement intact et sa tumeur ne devient apparante que plusieurs semaines ou mois après la métastase.*"

Our experience with the two cases reported herein fits perfectly into this pattern. In each, total surgical thyroidectomy, carried out as soon as the diagnosis had been established by biopsy of the osseous metastasis, rendered possible a complete anatomical survey of the thyroid gland at the time of first recognition of the thyroid lesion, an opportunity not heretofore recorded, and one which answers to some degree the criticism of "incomplete" examination of the primary tumor. Data on surveys and therapy with I^{131} are also presented.

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REPORT OF CASES

Case 1

I. S., age 50, a white, married, housewife, was hospitalized on June 4, 1952 because of pain in the right chest for "several weeks". The pain had been more severe and localized to the lower side of the right chest following a sneeze two weeks prior to admission. On physical examination, a very tender area about 2 cm. in diameter was noted in the right lower thorax along the posterior axillary line, at the level of the 11th rib. There was no local swelling or significant change in the overlying skin. The thyroid gland was not palpable. Radiographic examination of the ribs revealed an expanding, destructive lesion involving the right 11th rib in the posterior axillary line, "strongly suggestive of neoplasm" (Fig. 1A). There were no other osseous lesions radiographically. Serum alkaline phosphatase was 3.4 units. On June 11, 1952 the involved portion of the right 11th rib was excised (Fig. 1B). *Gross Description of Specimen:* The specimen was a resected portion of rib, 6 cm. long. Approximately in its midportion, there was a fusiform swelling, 1 cm. in greatest width, covered by periosteum. The cortex was markedly thinned out over the swelling and the cortical bone was partly destroyed, with an area of fracture. On section, the appearance was that of an expanding tumor replacing the medulla and cortex. The neoplasm was composed of red-brown glistening tissue and appeared to be circumscribed (Fig. 1C). *Microscopic Description:* Sections revealed very little original bone in the tumor areas; two small trabeculae and a portion of periosteum could be recognized. The remainder of the section consisted of very well differentiated thyroid tissue, being constituted of small and medium-sized acini which were lined by cuboidal cells and which frequently contained colloid. The nuclei were uniform in size, shape and staining reaction, and were free of mitotic figures or significant atypism. The acini were supported by a fibrous stroma which was quite normal in appearance and did not suggest histologically the desmoid stromal reaction commonly associated with malignant epithelial neoplasm (Fig. 1D). *Diagnosis:* Metastatic "adenoma" (thyroid primary) of the rib.

The basal metabolic rate was minus 10 per cent. Four millicuries of I^{131} were administered and 48 hours later, on June 23, 1952, a total thyroidectomy was performed. *Gross description of specimen:* Specimen consisted of a totally resected thyroid gland. Its transverse diameter was 6.5 cm. In the lower portion of the right lobe a soft nodular mass the size of a hazelnut could be felt. Section through the right lobe revealed a spherical, fleshy, pale, tan, node measuring 1.2 cm. in diameter. It was circumscribed and completely surrounded by normal thyroid tissue. Except for a tiny cystic area, the nodule was solid. The remainder of the thyroid gland appeared normal. On the posterior surface of the left lobe, attached to the capsule, there was a tiny yellow nodular body resembling parathyroid gland (Fig. 2A). *Microscopic Description:* Sections revealed an encapsulated tumor of essentially adenomatous structure. A study of multiple blocks across the entire lesion revealed occasional areas in which groups of acini were present in the capsule; these appeared to represent an intermingling of the fibrous capsule with the peripheral part of tumor. Invasion of blood vessels or of surrounding normal thyroid parenchyma was not observed. The tumor was composed of very well-differentiated acini of medium size; most of them were abundantly filled with typical colloid material (Fig. 2B). While most of the tumor conformed to the above description, there were certain variants present. In a few areas the follicles were small and empty of colloid material. In still other areas there was a change to very small glandular structures which only occasionally contained droplets of colloid material. The nuclei were everywhere uniform in size, shape and staining; mitotic figures were exceedingly rare. Near the center of the tumor there was a small area of dense scarring. *Diagnosis:* So-called metastasizing "adenoma" of the right lobe of the thyroid gland.

About 24 hours after operation the patient developed manifestations of tetany. Blood calcium values of 8.9 mg per cent and 9.6 mg per cent were recorded. Her postoperative course was otherwise uneventful and she was discharged on June 30, 1952.

On August 20, 1952, a test dose of 1.8 mc was administered and survey with the directional

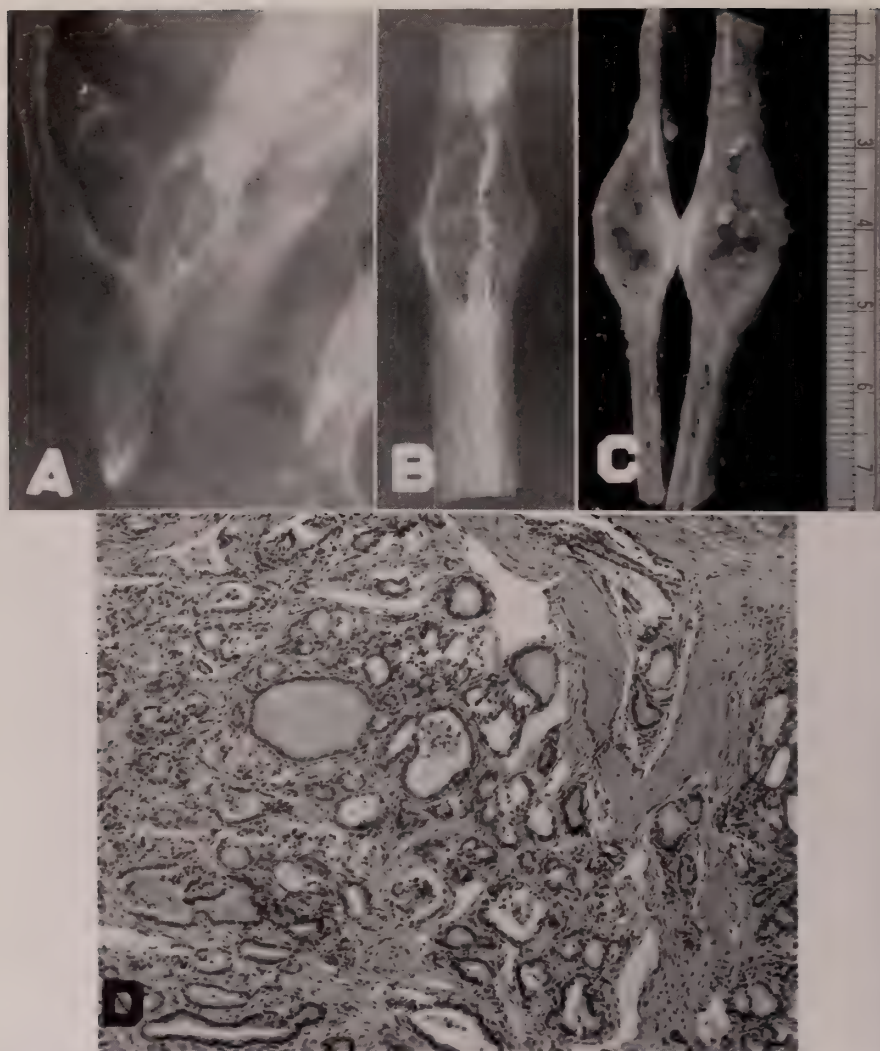


FIG. 1-A. *Case I*: Radiograph showing expanding, destructive, osteolytic lesion in right 11th rib.

FIG. 1-B. *Case I*: Radiograph of surgically resected portion of right 11th rib showing details of expanding osteolytic lesion with fracture.

FIG. 1-C. *Case I*: Gross photograph of cross section of resected portion of right 11th rib showing fusiform swelling with expanding destructive tumor sharply delineated at either end from normal rib. The cortex is thinned and in areas is broken through. The tumor tissue on section was cellular, moist, and was reddish-brown in color.

FIG. 1-D. *Case I*: photomicrograph $\times 120$ of section of metastatic tumor in right 11th rib. Osseous trabeculae above right. Marrow completely replaced by well-differentiated thyroid tissue. Many acini are filled with typical colloid.

Geiger counter failed to reveal any site of uptake suggestive of metastatic tumor. Nevertheless, prophylactic therapeutic doses of 81.3 mc (on August 23, 1952) and 15.0 mc (on August 29, 1952) were administered. Between her discharge on June 30, 1952 and her admission in November 1956 for pain in the opposite lower (left) chest, her course was uneventful except for rather severe hypoparathyroid tetany which required careful control with hytakerol

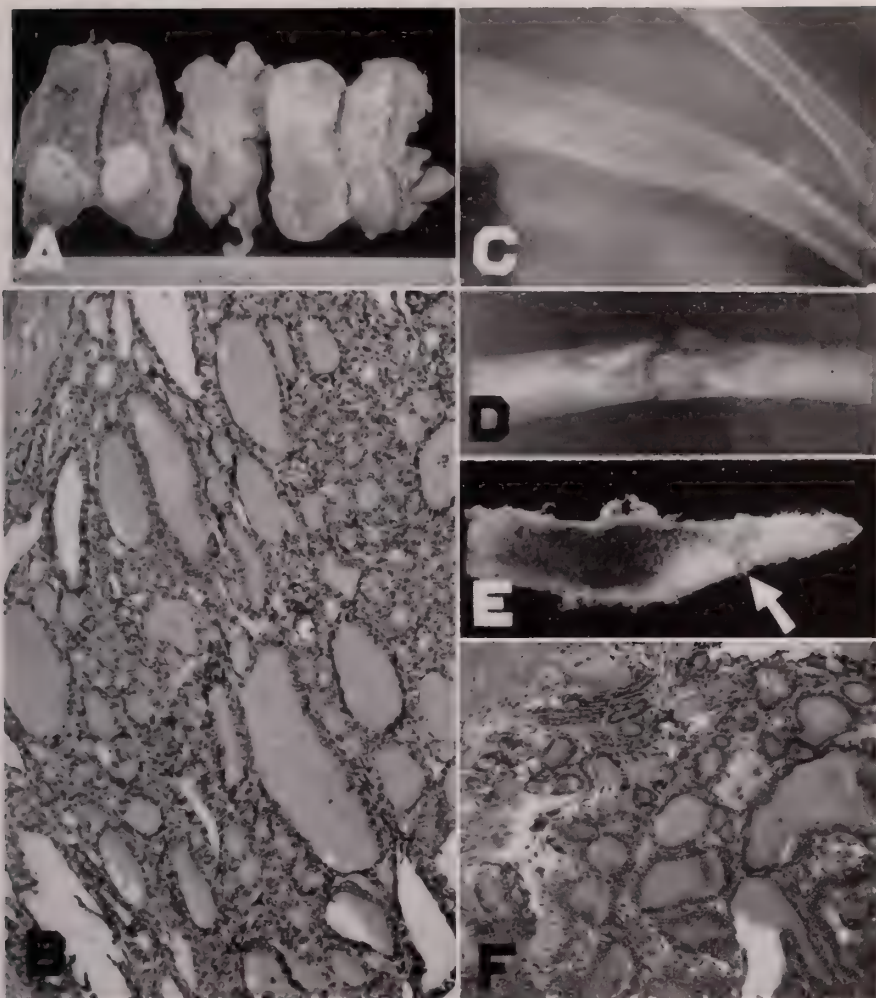


FIG. 2-A. *Case I*: Entire thyroid gland, right lobe, isthmus, left lobe (from left to right). In the lower pole of the right lobe there is a sharply circumscribed tumor 1.2 cm. in diameter. It is homogenous, pale, with two tiny cystic areas. Its color was light tan.

FIG. 2-B. *Case I*: Photomicrograph $\times 120$ of tumor in lower pole of right lobe of thyroid gland. Small portion of capsule at upper left. Tumor is composed of well-differentiated typical thyroid acini containing abundant colloid material. Histologic pattern is that of adenoma.

FIG. 2-C. *Case I*: Radiograph of left 9th rib. Five years after first admission. Area of slightly expanding, destructive, osteolytic, metastatic involvement.

FIG. 2-D. *Case I*: Radiograph of surgically resected portion of left 9th rib showing additional details of metastatic involvement including fracture.

FIG. 2-E. *Case I*: Gross photograph of cross section of portion of surgically resected left 9th rib. Normal marrow to the left, area of tumor tissue with area of fracture to the right (arrow). Color of the tumor grossly was reddish-brown.

FIG. 2-F. *Case I*: Photomicrograph $\times 120$ of section of metastatic tumor in left 9th rib. Portion of osseous trabeculum above left. Replacement of marrow by metastatic thyroid tumor. The acini are well differentiated; most of them are filled with colloid.

and calcium gluconate or calcium lactate. In November, 1956, pain, especially on deep breathing, appeared in the left chest and she was readmitted on November 10, 1956. Physical examination revealed intense tenderness over the 9th left rib in the anterior axillary line. However, radiological examination failed to demonstrate evidence of fracture or of metastatic tumor and the patient was discharged on November 26, 1956. On December 20, 1956 a tracer dose of 0.05 mc of I^{131} was administered. Total survey with the directional Geiger counter failed to disclose any evidence of functioning metastatic tumor. On January 3, 1957, she was admitted again because the pain in the left chest had persisted and increased. Radiological examination of the ribs now revealed a lytic area in the left 9th rib in the anterior axillary line (Fig. 2C). This lesion was excised on January 7, 1957 (Fig. 2D). *Gross Description:* The specimen consisted of a resected portion of rib measuring 9 cm. in length. Near the middle of the specimen, there was a cortical defect and fracture. The defect measured about 0.5 cm. at its widest portion. On section, the region of the defect and fracture was seen to be the site of a circumscribed, reddish-brown, moist tumor sharply separated from the surrounding normal marrow and cortex (Fig. 2E). *Microscopic description:* Sections revealed metastatic tumor similar to that described in the sections of the lesion excised from the right 11th rib. The acini were well differentiated, frequently filled with colloid material, and lined by high cuboidal cells (Fig. 2F). Mitoses could not be found; the nuclei were pale and uniform in size and shape. The stroma was composed of mature connective tissue. The cortex was directly penetrated by the tumor as far as the periosteum. Periosteal muscle and fat attached to the specimen were not infiltrated. *Diagnosis:* Portion of rib with metastasis originating in so-called metastasizing "adenoma" of thyroid gland.

The postoperative course was uneventful and the patient was discharged on the fifth postoperative day. Her condition is unchanged as of May 1, 1957.

Case 2

H. L., age 66, white, male, was admitted to Lebanon Hospital on September 19, 1955 complaining of pain for five months and a swelling for three or four weeks in the region of the left hip. On examination, a mass the size of a tennis ball was noted over the left anterior superior iliac spine. The tumor was smooth, slightly tender, and "had the consistency of cold lard". There was no mention of pulsation or thrill. The thyroid gland was not examined. The clinical diagnosis was lipoma or liposarcoma. Radiographic examination of the left pelvis on admission revealed a destructive process involving the lateral portion of the body of the left ilium (Fig. 3A). The lesion extended into the soft tissue and contained calcific flecks.

On September 20, 1955, surgical removal of the tumor was attempted. As soon as the mass was incised, profuse hemorrhage occurred. The blood pressure fell to 80/60 and an immediate transfusion of 500 cc was given. Biopsy specimen was obtained, the wound cavity was tightly packed with oxyeel, and after some difficulty, the hemorrhage was controlled. *Gross description:* Specimen consisted of an irregular fragment of tissue measuring approximately 5 by 4.5 by 3 cm. The consistency was soft, rubbery, and the external surface consisted of dissected tumor. On section, the appearance was moist, pale tan in color, and there was a suggestion of greasiness. There were multiple focal hemorrhages. Bony or calcific material could not be recognized grossly. Multiple sections at various levels were more or less uniform in appearance. *Microscopic description:* Sections revealed the tumor to be composed of tissue resembling thyroid gland. There were a few slender atrophic osseous trabeculae scattered throughout the section, but no marrow or fat. The epithelial elements consisted of well differentiated acinar structures, mostly small in size, lined by high cuboidal, typical thyroid acinar epithelium and usually filled with homogeneous acidophilic colloid material. This tissue differed, however, from thyroid gland in the almost total lack of stroma. Its structure was rather cavernous, the vascular channels being lined by a single layer of endothelial cells in direct approximation to the tumor acini. The nuclei of the epithelial cell were remarkably uniform in size, shape, and staining reaction. Mitoses were very rare (Fig. 3B). *Diagnosis:* Metastatic "adenoma" (thyroid primary) of the iliac bone.

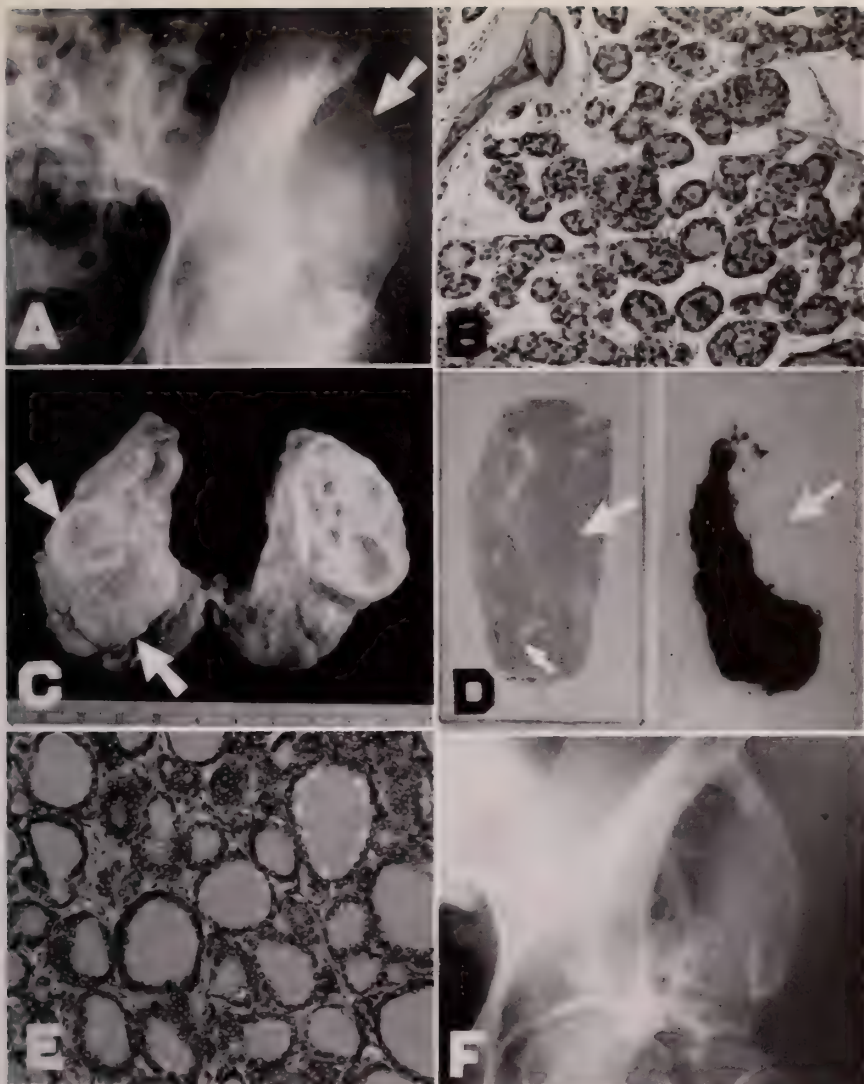


FIG. 3-A. *Case II*: Radiograph of left side of pelvis showing metastatic tumor involving lateral portion of body of left ilium. The tumor has expanded into the soft tissue area but is still covered by periosteum (arrow). Markings produced by the postsurgical dressing are evident.

FIG. 3-B. *Case II*: Photomicrograph $\times 100$ of section of metastatic tumor of ilium. Partially atrophic osseous trabeculum above left. Marrow is replaced by metastatic well-differentiated thyroid tumor; many acini are filled with typical colloid material. The glandular tissue is supported by an extremely rich sinusoidal vascular framework which appears emptied of blood in the photomicrograph.

FIG. 3-C. *Case II*: Entire thyroid gland. Two tumors are present, one in the lower half of the right lobe (on the left side of photo), one in the upper half of the left lobe (on the right side of photo). The latter is a densely encapsulated, hyalinized and partially calcified adenoma with areas of cystic degeneration. The tumor in the lower half of the right lobe is considered to be the source of the metastatic disease. It contains a spherical area of fibrosis, hyalinization and calcification in its upper portion (arrow). The lower portion (arrow) of the tumor is a circumscribed cellular tan neoplasm whose histologic pattern is that of a well-differentiated adenoma of thyroid gland (see Fig. 3-E below).

FIG. 3-D. *Case II*: Contact radioautograph (right) of portion of thyroid tumor (left), $\times 14$. The tumor-bearing area is shown at arrow. This area is surrounded by a shell of normal thyroid tissue containing "satellite" nodule of tumor (arrow). In this photo the localization of I^{131} after the test dose is seen to be restricted to the shell of normal thyroid parenchyma. The tumor-bearing area (arrow) does not show any pick-up.

FIG. 3-E. *Case II*: Photomicrograph $\times 120$ of tumor of thyroid in Fig 3-C, lower arrow. The acini are very well differentiated and abundantly filled with colloid material.

FIG. 3-F. *Case II*: Radiograph of left side of pelvis taken on March 6, 1957, 18 months after the radiograph shown in Fig. 3-A. Healing of eroded cortex of left ilium and calcification of the tumor are shown. During this period the patient received 8 therapeutic doses of I^{131} and has always shown a concentration ratio of the lesion to control of 10:1.

Palpation of the thyroid gland revealed a firm mass in the inferior portion of the right lobe. Radiological survey of the entire osseous system failed to disclose any other metastatic lesion. The basal metabolic rate was +3 per cent on September 26, 1955. On September 28, 1955, a tracer study with I^{131} revealed the following: 24 hour uptake by the thyroid gland was 42 per cent of administered dose (high normal); uptake over the right lobe was less than over the left lobe; survey with the directional Geiger counter in the region of the left hip did not reveal any uptake.

Total thyroidectomy was performed on October 4, 1955. *Gross description of specimen:* The specimen consisted of the entire thyroid gland. The right lobe measured approximately 7 by 5 by 4 cm. The entire capsule was present. The parathyroid glands could not be found. Section revealed a very well circumscribed, tannish, multi-nodular tumor, 3 cm. in diameter, in the inferior portion of the lobe. Several smaller nodules ranging from 0.2 to 0.4 cm. in diameter and similar in appearance to the large mass were scattered in the remainder of the lobe. Near the center of the large tumor, there was an area 2 cm. in diameter of somewhat different appearance. This area was spherical in shape, traversed by coarse fibrous trabeculae, and enclosed by a thick capsule. Its gross appearance suggested an old encapsulated adenoma with secondary fibrosis and hyalinization. The left lobe measured approximately 6 by 4 by 3 cm. The capsule was intact. The parathyroid glands could not be found. A firm nodule was palpable in the upper pole; on section, this nodule measured 4 by 2 cm. It was well encapsulated and contained numerous small cystic areas separated by glistening white fibrous trabeculae. There was some calcification of the capsule. The gross appearance was that of an old, cystic, adenoma with fibrosis and hyalinization. There was no gross abnormality in the isthmus portion (Fig. 3C).

The uninvolved thyroid parenchyma in both lobes and in the isthmus had a reddish-brown, moist, fleshy, appearance with grossly visible globules of colloid. *Microscopic description:* Sections of the main tumor area in the right lobe revealed the pattern of well differentiated adenoma of thyroid gland. The acini were small to very small in size, lined by tall cuboidal epithelium, and usually contained typical colloid material. The nuclei were large, vesicular, and uniform in size, shape, and staining reaction. Mitoses were very rarely found (Fig. 3E). Occasional tiny necroses were present. Most of the follicles were arranged in close contact with one another, but occasional areas presented intervening fibrous separation. There was a thin fibrous capsule which at several points was invaded by "adenoma". A rare capsular vein contained clusters of tumor cells.

Sections of the encapsulated nodule described in the center of the main tumor in the right lobe presented a mixed appearance which was interpreted as the combination of an old, fibrosed adenoma and the metastasizing "adenoma". The old lesion was recognized by the thick hyalinized capsule, cholesterol deposits, and atrophic remnants of adenoma. One small area of the tumor presented the pattern of a rich sinusoidal capillary bed whose endothelial cells were closely applied to the glandular structures in a manner similar to that described in the specimen from the left iliac bone. Several smaller, "satellite" nodules of adenoma-like tumor identical in pattern with the main tumor were present in the thyroid parenchyma nearby. All of the nodules observed were sharply demarcated from surrounding thyroid parenchyma, and, in the details of their histologic structure, resembled closely the adenomatoid pattern described above. The only exceptions were the small area with cavernous vascular bed (described above) and a rare tiny area with trabecular architecture.

Sections of the nodule in the upper pole of the left lobe revealed a histological pattern consistent with the gross impression of cystic adenoma with secondary fibrosis, hyalinization, and calcification. This lesion was sharply demarcated from the surrounding parenchyma by hyalinized, fibrous capsule.

The uninvolved residue of thyroid gland in both lobes and isthmus was not remarkable. *Diagnosis:* So-called metastasizing "adenoma" of the right lobe of the thyroid gland; old encapsulated adenomas of right and left lobes.

The postoperative course was uneventful and the patient was discharged on October 10, 1955.

A survey after thyroidectomy revealed that the uptake of I^{131} over the thyroid region was about 2.7 per cent at 24 hours after the dose, a result consistent with virtually complete removal of thyroid tissue. The metastasis in the pelvis, however, was now found to function. Total survey with the directional Geiger counter revealed a concentration ratio of the lesion to control area of 7:2. Between October 26, 1956 and the present time, eight therapeutic doses of I^{131} have been administered. Following the first therapeutic dose, the concentration ratio has always been 10:1 or more.

The patient was last seen on March 6, 1957, when he appeared to be in good health. The residual mass in the left ilium measured approximately 7 by 10 cm at that time, and radiographic examination demonstrated progressive calcification and/or ossification of the metastasis with some filling-in of the previously eroded cortex of the bone.

DISCUSSION

Simpson (6), in one of the most widely quoted studies on the subject of benign metastasizing goiter, analyzed seventy-seven cases collected from the literature and added three of his own. He concluded that the entity did not really exist, that it was based upon a misconception growing out of inadequate histological study of the primary lesions, that all cases were in fact instances of ordinary carcinoma of the thyroid gland, and that the concept of benign metastasizing goiter should be abandoned. In his own material, however, Simpson was able to examine the thyroid gland microscopically only once; the other two cases were interpreted as primary carcinoma of the thyroid gland on the basis of data from the office records of physicians and death certificates. Another paper which rejects the concept of metastasizing goiter, that of Berard and Dunet (7), concludes that serial sections would always establish the histologically malignant structure of the thyroid lesion. The authors reached this conclusion by a critique of previously published cases and their own single experience, one in which the pathologist's description of sections of the thyroid nodule noted foci of stromal infiltration by neoplastic cells in an otherwise benign-looking, encapsulated, adenomatous nodule.

Cohnheim's original report in 1876 (2) was based upon a careful histological study of the entire thyroid gland at autopsy, and included a very adequate illustration of the microscopical pattern of ordinary colloid goiter. Langhans (3) confirmed fully the observations by Cohnheim, and comprehensive reviews of the literature by Joll in 1923 (8) and by Wegelin in 1926 (1), after thorough weeding-out of instances lacking adequate histological study of the primary tumor, acknowledge the existence of metastasizing lesions of the thyroid gland whose histological pattern appears to be entirely benign. Wegelin (1926) accepted fifteen cases out of the literature prior to 1926 and added two of his own. Our two cases are the first in which the pathologist was given the opportunity to examine the entire thyroid gland immediately after the establishment of the diagnosis of metastatic thyroid tumor to bone (Figures 2A, 3C). Previous cases had been subjected to partial, hemi-, or subtotal thyroidectomy (9-11). While we did not find it practical to prepare serial sections of these thyroid glands, it is clear that painstaking search through multiple blocks disclosed essentially benign patterns (Figures 2B, 3E). Mitotic figures were very rare in both primary tumors and metastases. The degree of maturity and colloid content of the acini conformed

to those of benign adenoma, and while a small focus of trabecular architecture was found in an occasional section of the lesions in the right lobe in Case 2, there were no areas of undifferentiated, papillary, anaplastic, infiltrating, or other obvious histological pattern of malignancy to be found in either case.

With regard to the question of vascular invasion, a rare blood vessel was found containing clusters or fragments of tumor cells in Case 2. We hesitate, however, to accept this finding as evidence of vascular invasion because of the possibility of artefactual entry of tumor into blood vessels as a result of the excessive manipulation during the surgical procedure and the processing of the specimen in the laboratory. Had these fragments of tumor existed in the vascular lumina prior to surgery, they should have been swept along by the force of the blood current, and carried, if in arteries, distally to other areas of the thyroid gland, or if in veins, to the lungs. Furthermore, we observed only free fragments in the lumina of otherwise normal vessels; there was no evidence of direct penetration of vascular walls (12).

A finding which deserves more weight in assessing the malignant character of thyroid nodules is intrathyreoglandular spread. In our Case 2, several smaller nodules were present in the right lobe at varying distances from the main tumor (Figure 3D, lower arrow). These may have resulted from such different mechanisms as direct migration across normal parenchyma, penetration of arteries with distal embolization within the thyroid gland, or multifocal primary origins. The histological pattern of all of these nodules was that of "benign adenoma". Whatever the mechanism of their origin, the fact of this dissemination within the right lobe of the thyroid gland offers additional testimony to the malignant character of the lesion. Capsular invasion was also present in this case.

In Case 1, it seems doubtful to us that a histological diagnosis of malignant tumor of the thyroid gland would have been entertained in the absence of the knowledge of the metastasizing potential which had already manifested itself clinically.

The actual histological structure of these thyroid tumors at the time of inception of the first metastasis will probably never be known, since the thyroid lesion cannot be discovered until months or years later (13). In our Case 1, a proved period of five years was required for the development of the lesion in the left ninth rib.

Pulsation, sometimes accompanied by murmur and thrill, is a fairly common clinical feature of the osseous lesions (4, 10, 11, 13). This was not described in the clinical records of our cases, but may have been missed. In Case 2, the lesion was so vascular that incision caused copious and almost uncontrollable hemorrhage, with near-fatal exsanguination. The histological pattern of this metastasis was characterized by a sinusoidal or lacunar capillary spongework supporting the epithelial cells without recognizable intervening stroma (Figure 3B). Ewing (14) noted the intimate relation of acinar epithelium to capillary endothelium in the thyroid gland and suggested that this may offer a mechanical basis for the entry of epithelial cells into the blood stream.

An old, encapsulated adenoma, extensively fibrosed and hyalinized, was

present in the center of the mass in the right lobe of the thyroid gland in Case 2 (Figure 3C). Rosenthal and Willis (15) reported a similar experience and considered the possibility of the development of a malignant tumor from a long standing adenoma.

It is difficult at the present time to evaluate objectively the extent to which the course of the disease in our patients may have been deviated by surgery and therapeutic I^{131} . Not enough is known regarding the extremes of the natural evolution of this tumor to permit us to ascribe definitive effects to therapy. Although Case 1 has progressed very slowly over a period of five years, with only one new metastatic lesion after resection of the thyroid gland "behind" the original metastasis, comparable patterns of slow evolution were documented prior to the isotope era. Over a period of twelve years, a patient who has received no therapy and is currently under observation, has revealed no significant change in a biopsy proved metastasis of mature thyroid tissue in the humerus with a clinically normal thyroid gland (16).

Frazell and Foote (17), who found ten cases belonging to this group in a series of 301 cases of thyroid cancer, also stressed the very slow natural evolution, and reported one patient alive after twenty-two years. Our second patient has not developed additional clinical manifestations of tumor in eighteen months, and the residue of the metastasis in the left iliac bone is now partly calcified and appears arrested (Figure 3F). This lesion has repeatedly revealed, by directional Geiger counter survey, strong (10-1) concentration of I^{131} in comparison to the control area. In Case 1, on the other hand, the second osseous metastasis developed in spite of therapeutic doses of I^{131} , and directional Geiger counter survey failed to reveal any uptake by histologically mature metastatic thyroid tissue in this athyreotic patient.

The tendency to ignore regional lymph nodes and to favor dissemination to distant bones is very characteristic of metastasizing "adenoma" of the thyroid gland. Langhans (18) never observed invasion of regional lymph nodes. It is necessary to postulate hematogenous transport of small, possibly single cell fragments across the pulmonary capillary bed to the bones. Cohnheim (2) had observed grossly the invasion of a tributary of the inferior thyroid vein. The overwhelming predominance of osseous localization of the earliest metastases presupposes further some form of special organ host factor which is instrumental in rejecting or suppressing tumor emboli which reach tissues other than bone. This idea was first expressed by Cohnheim (2) and was concurred in by Wegelin (19).

The conclusion seems inescapable that in metastasizing "adenoma" of the thyroid gland we are dealing with an unusual category of neoplastic disease in which the malignant character of the primary tumor does not find the usual histological expression. That this is so should not be too surprising. The natural harmony between biological behavior and histological structure of neoplasms has familiar exceptions, such as, for example, papillary cystadenoma of the ovary and leiomyoma (20). Graham (21) and Wegelin (19) agreed that the microscopical appearance of cells, structure and colloid content of follicles, and

mitoses, are unsatisfactory guides to the malignant character of thyroid nodules. Our cases confirm this opinion. On the other hand, they found that capsular, parenchymal, and vascular invasion (particularly the last) correlated better with malignant behaviour. In our cases, capsular and parenchymal invasion were found in Case 2. We were unable to find unequivocal evidence of vascular invasion in either case. The last is in disagreement with the experience of Warren (22) and of Graham (21). The term "adenoma" may justifiably be retained for historical reasons, the quotation marks qualifying its meaning and acknowledging the special character of this tumor as a malignant neoplasm with metastatic potential despite a histologically benign pattern.

SUMMARY

1. The concept of metastasizing "adenoma" of the thyroid gland is confirmed. It is a clear-cut clinico-pathological neoplastic complex characterized by initial clinical manifestation as a destructive, often pulsating tumor of bone, usually misdiagnosed as osteosarcoma. The primary tumor in the thyroid gland is clinically silent and may only be discovered after histological study of the metastasis in the bone. Examination of the thyroid gland discloses a circumscribed nodule or nodules whose histological pattern of acinar structure is benign. Capsular, parenchymal, and vascular invasion may be, but are not necessarily present. Regional lymph nodes are usually not involved. The rate of natural evolution of the disease is very slow, and may extend over many years, even without therapy.

2. Although the microscopic structure of the metastatic deposits in bone in our two cases was that of well-differentiated thyroid tumor, only one picked up tracer I^{131} after total thyroidectomy. There is insufficient evidence at the present time to assess the therapeutic effectiveness of I^{131} in this disease.

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LIPOGRANULOMATOSIS

A NEW LIPO-GLYCO-PROTEIN "STORAGE" DISEASE¹

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In selecting a paper for inclusion in this volume honoring a friend, the distinguished pathologist and inspiring teacher, Dr. Paul Klemperer, the decision to present in detail our experience with lipogranulomatosis was reached because this paper illustrates some of the techniques in which Dr. Klemperer was a leader. These include the recognition of a new problem by biopsy, guidance of subsequent clinical investigation, detailed gross and microscopic postmortem studies with the aid of histochemical methods and, finally, definition of the nature of the abnormality in chemical terms. The goal of such studies is the determination of the seat and the cause of disease, the elucidation of the nature of the process, the genesis of the lesion, and the effect upon the organism and its components. And from all of this, there is sought a basis for rational therapy and, hopefully, prevention. In these areas, among others, Dr. Klemperer is an acknowledged master. And so, this paper is submitted with deep respect and affection for him.

At a Mayo Foundation lecture, May 1, 1947, one of us (S. F.) summarized his studies of some twenty years on the lipid metabolic disorders. A sharp differentiation was made between a group of true metabolic disorders, such as Gaucher's, Niemann-Pick and Tay-Sachs diseases, and another group of disorders, which he believed to be variations of the same underlying process—Hand-Schüller-Christian disease, Letterer Siwe disease, and eosinophilic granuloma of bone. He suggested that the second group were not metabolic disorders, but rather inflammatory in the broad sense of the term, with an initial granulomatosis process characterizing the lesion, followed later by partial lipidization.

As preparation for this lecture proceeded, these two groups of disorders appeared to grow further and further apart, until it became difficult to recall just why Hand-Schüller-Christian disease could ever have been placed in the classification of lipid metabolic disorders. Unfortunately for the purity of classifications made without full understanding of etiologic factors, the study of an infant by biopsy, clinically and at postmortem examination, a few months before this lecture was given, disclosed what appeared to be a new disease entity bearing important resemblances both to Niemann-Pick disease and to the Hand-Schüller-Christian and Letterer-Siwe group of disorders. In the Mayo Foundation lecture, therefore, a report of these new findings was made and placed as

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a possible bridge between what had appeared to be two etiologically unrelated groups of disorders in the young.

Since the findings described under the term lipogranulomatosis were unique in our experience, and because nothing identical could be found in the literature, a report was made before the American Pediatric Society, in order to stimulate the interest of other observers (S. F.) (1). This report included additional observations on two siblings with clinical and pathological findings similar to those of the infant mentioned. The present paper records the detailed clinical and pathological findings made with the valuable collaboration of Jonathan Cohen, and the studies of L. Lahut Uzman, who was able to characterize, chemically, the materials accumulated in an abnormal fashion in the tissues of two of these patients. This detailed report has been delayed in the hope that more could be learned about the occurrence, nature, and cause of this new disorder. In May, 1956, on a visit to Stockholm, a discussion was heard by Dr. Rolf Zetterstrom of the University Children's Hospital, of his extensive clinical investigation of an infant with findings identical to those which we describe in this paper. Dr. Zetterstrom's studies on his patient, who is still surviving, have not yet been published.

CASE REPORTS

Case 1

J. B. #309642. This girl, the third child of healthy parents, was born by Caesarean section six weeks after term and weighed 6 lbs. 13 oz. at birth. Except for an upper respiratory infection at the age of three months, which responded to penicillin therapy, she was well until her present illness began. When she was four months old she developed redness, excessive sweating, and hyperesthesia of the hands and feet, and in the next few weeks, a brown, desquamating dermatitis appeared, with cracking and crusting of the interdigital creases, followed by a gradual swelling, which was accentuated at the joints. Meanwhile, her voice became hoarse and her breathing noisy and rasping, accompanied by sternal retraction. She became irritable and anorexic, failed to gain weight, but remained afebrile. During the next three months, there was progressive involvement of all joints by swelling and pain, and flexion contractures appeared at the fingers, wrists, elbows, hips and knees. The dermatitis disappeared during this time, but the hoarseness progressed to aphonia, and the irritability and anorexia continued. There was only one febrile episode, lasting a few days. Until hospitalization elsewhere at the age of nine months, the diagnosis of acro-dynia was entertained, but after a complete work-up, it was thought that Still's disease was more probable because of the increasing prominence of the joint involvement.

The positive physical findings at that time were as follows. The infant lay motionless, with head turned to the right. There was marked facial asymmetry; passive motion of the neck was limited and painful and the infant would go through the motions of crying, but made no sound. There was sternal retraction on inspiration, but the lungs were clear to auscultation and roentgenogram. The liver was palpable 3 cm. below the costal margin. Slight generalized lymph node enlargement was palpable. All four extremities showed swelling, limitation of motion and flexion contractures at all joints, which were tender but not reddened.

Laboratory examination revealed an elevation of the leucocyte count to between 17,000 and 36,000 per cu. mm. The sedimentation rate and the remaining laboratory procedures, including roentgenograms, were not remarkable.

During one month of hospitalization, the child improved slightly under penicillin ther-



FIG. 1. *Case 1.* The nodules on the wrist, knuckles and index finger are evident. The abdominal skin also contains nodules.



FIG. 2. *Case 1.* There is destruction of the sigmoid notch of the ulna and some subluxation of the elbow joint due to distension.

apy. The joint swellings subsided somewhat and small para-articular nodules could be palpated. One large suboccipital nodule also was felt. She continued at the same weight and began to run a low-grade intermittent fever. She was admitted to The Children's Medical Center, Boston, at the age of eleven months, where physical examination was essentially as above, except that the lungs now showed typical asthmatic breath sounds and there was marked nodularity of the subcutaneous tissue of the abdomen and thorax, as well as over the joints (Fig. 1). These had become fusiform and showed more limitation of motion. Laboratory tests continued to show slight but constant leucocytosis, and the sedimentation rate was now elevated. Cultures of the nasal, pharyngeal and tracheal secretions yielded a variety of organisms, none of which was constantly present. The roentgenograms of the extremities showed a loss of bone substance in many areas adjacent to joints, e.g., the acromion, the sigmoid notch of the ulna (Fig. 2) and the vertebral pedicles. Marked articular swelling was evident and the left hip was dislocated by articular distension. The lungs, by roentgenograms, showed slight diffuse infiltration. A laryngoscopic examination disclosed fixation of the vocal cords and a tracheotomy was performed, with some temporary increase in respiratory comfort. At biopsy, a nodule at the wrist and an area of bony destruction in the ulna showed granuloma containing large numbers of foam cells.

The child's course in the hospital was gradually down-hill, with frequent febrile episodes and progressive respiratory involvement. Terminally, she weighed 16 lbs. 3 oz., and was fourteen months old.



FIG. 3. (Case 1. Heart. The thickening of the chordae tendineae and nodular swellings at the attachment of the mitral valve are evident.

Autopsy Findings. (A46-244. Dec. 21, 1946) The outstanding process, one of accumulation of foam cells and granulomatous reaction, involved the following organs and regions: heart, lungs, lymph nodes, joints, subcutaneous tissue, and the loose areolar tissue surrounding many viscera, e.g., thyroid, tongue, tonsils. The *heart* was normal except for a few yellow-brown nodular areas on the pericardium and on the valves and chordae tendineae (Fig. 3). On section, these nodules consisted of large numbers of macrophages and foam cells, surrounded by and intermingled with areas of granuloma formation. Occasional foci of acute inflammation were seen adjoining areas of necrosis within the granuloma. The foam cells did not occur in masses but were numerous and stained faintly with Scharlach R. Some macrophages contained ingested nuclear fragments as well as lipoid material. The *lungs* were resilient and lacked crepitus except for a few emphysematous lobules. A few nodular thickenings were present in the pleura. The hilar nodes were large, discrete and fleshy. On section, the pleural nodules were identical with those in the pericardium. The lung parenchyma was diffusely infiltrated by foam cells and granuloma. Foam cells, in all stages of degeneration, filled the alveoli, and the interalveolar septa contained, in addition to these cells, many macrophages and granulomatous elements. The *gastrointestinal tract* was notably free of lesions. The *kidneys, pancreas, adrenals, spleen*, and *pelvic organs* also were normal. The *liver* was not enlarged, and showed only slight fatty metamorphosis. The gall bladder, while



FIG. 4. *Case 1.* The hip joint shows extensive thickening of the ligamentum teres and the capsule. Pannus covers a large part of the acetabulum.

grossly normal, contained many foam cells in the submucosa but no granulomatous elements. The epithelium of the *larynx* was edematous and the cords and aryepiglottic folds thickened. Microscopically, granulomatous involvement of the cricoarytenoid and aryteno-corniculate joints was of such degree as to obliterate the joint cavities. Foam cells were interspersed in the granuloma. Diffuse chronic, inflammatory reaction involved the entire length of the trachea and esophagus and pharynx, and was most marked in the loose alveolar tissue surrounding these structures and in the subepithelial connective tissue layer. The *lymph nodes* in the hilar, cervical, axillary, mesenteric and para-aortic regions were all enlarged, fleshy and discrete, and microscopically showed depletion of lymphocytes and replacement by lipid-containing macrophages. All the *joints* which were examined showed marked limitation of motion due to infiltration of the capsules by a firm rubbery nodular tissue which covered part of each joint cartilage as pannus, and extensively involved the synovial membrane and the nearby connective tissues (Fig. 4). Some joint spaces were reduced to residual slits with all of the articular cartilage firmly encased in pannus. In the fingers, a continuous nodular infiltration of the interphalangeal joints, tendon sheaths and subcutaneous tissue was evident. Microscopically, the infiltrative tissue was identical with that described above, with granulomatous elements predominating. Occasionally, there was a superficial resemblance to a rheumatoid reaction, because of necrosis of collagenous elements in the granuloma, but the foam cells, the absence of palisading, and the more widespread involvement distinguished the two processes. The *bone marrow* contained increased numbers of macrophages but no foam cells or granuloma were seen, except in those para-articular areas where bony involvement was continuous with the joint involvement. The *subcutaneous tissue* was involved in many areas. In some there was a diffuse increase in the number of macrophages with a few cells containing lipid. A few of foci of lymphocytes also were found. Other areas contained large nodules consisting of granuloma and foam cells. The *nervous system* showed no gross findings of note. Microscopically, in all sections examined, some nerve cells could be found exhibiting the pathologic change to be described. Sections of visceral ganglia, autonomic and posterior ganglia, and representative areas of the brain and spinal cord were examined. In the brain sections, the medulla showed the most involvement and the cerebral cortex the least. The nerve cell involvement consisted of an accumulation of a lipid material in the cytoplasm which was extensive enough to displace the nucleus to the cell wall in some cells. Some neurons were seen which were completely filled with lipid, and many were in various stages of degeneration or neuron

ophagia. Focal areas of gliosis and collections of gutter cells were seen. Satellitosis was seen infrequently. The changes in nerve cells were very similar to those found in Tay-Sachs disease.

Case 2

E. D. #3361341. A girl, the third child of healthy parents, was born at term after an uneventful pregnancy, and weighed 7 lbs. 9 oz. During the first week of life she apparently was well. She then became hoarse, but had no other symptoms until she was one month old, when she developed an upper respiratory infection with cough, labored respirations, and fever. This was treated successfully with penicillin but the hoarseness persisted. She was irritable and gained very little weight. During the second month of life she developed swelling and hyperaesthesia of the hands and feet. The swellings were diffuse at first, and tender, but not reddened. They became nodular about a week after their onset.

The infant was admitted to The Children's Medical Center, Boston, at three months of age. She weighed 8 lbs., 14 oz., was severely under-developed and under-nourished, and ran a low-grade fever. She moved her extremities infrequently and feebly, and her cry was weak and hoarse. The remaining positive physical findings were as follows. There was generalized limitation of motion of the joints of the extremities, particularly the wrists and fingers, with pain on motion of any kind. Large nodular swellings were palpable and visible at the wrists and proximal interphalangeal joints. The lungs showed coarse breath sounds, rhonchi, and a prolonged expiratory phase. The liver edge was palpated 4 cm. below the costal margin and the spleen could be palpated, but was not greatly enlarged. Slight, generalized lymph node enlargement was evident. The laboratory findings included a slight leucocytosis and elevation of the sedimentation rate. Cultures of the nose and throat yielded no constant organisms. Roentgenograms of the chest and extremities showed only the soft tissue swelling at the joints. Bronchoscopy revealed fixation of the joints of the larynx. At biopsy, a mass on one wrist showed granuloma with many foam cells.

The course of the infant in the hospital was one of intermittent low-grade fever and chronic, progressive involvement. She gradually became aphonic. Subcutaneous nodules appeared on the abdomen. Chronic, diffuse pulmonary infiltration became apparent both clinically and by roentgenogram when the infant was five months old. Prolonged ACTH therapy was tried without benefit. The contractures of the joints slowly became more fixed, despite traction, physiotherapy, and plaster splints. The infant did not gain weight, despite all types of dietary, antibiotic and supportive therapy. Her reactions to stimuli gradually diminished so that she often did not respond even to venipuncture. Her deep tendon reflexes disappeared, as did her pupillary reflex, while the Babinski remained positive. She was thought to have become blind, although her fundi remained normal. When the child was eleven months old, destructive lesions of bone adjacent to joints were evident by roentgenogram, and the soft tissue swellings and nodules had obviously become larger (Fig. 5). She declined slowly with more and more pulmonary involvement and she expired at the age of fourteen months, weighing 7 lb., 5 oz.

Autopsy Findings. (A51-121, May 9, 1951) The findings closely resembled those described in the previous case. Collections of foam cells and granuloma involved the following organs and regions: heart, lung, lymph nodes, joints, spleen, duodenum, colon, subcutaneous tissue and loose areolar tissue surrounding many viscera, *e.g.*, uterus, bladder, tongue, etc. Nodules, identical in appearance and staining reaction to those described above were found in the heart, at the mitral and tricuspid valves, the chordae tendineae and pericardium. The myocardium was normal. The lungs were covered with adhesions and appeared to be consolidated. Sections showed the alveoli and interalveolar septa and also the thick pleura to be infiltrated by foam cells and granuloma (Figs. 6 and 6 (a)). The foam cell component somewhat overshadowed the granulomatous process in extent, as compared with the involvement in the previous case. In the pleura, however, the reverse was true. The *gastro-intestinal tract* showed involvement by lipid-filled cells, particularly in the submucosa of



FIG. 5. *Case 2.* The nodules on the wrists and finger joints are the largest seen in this series and constitute a grotesque deformity of both hands.

the colon and of the duodenum surrounding the glands. These layers were crammed with large macrophages without granuloma—a finding not present in the previous case. In similar contrast, the *spleen* in the present instance, although not enlarged, was infiltrated with many foam cells without disturbance of the normal architecture. The *kidneys*, *pancreas*, and *adrenal glands* were normal. The *liver* was slightly enlarged and showed fatty metamorphosis. The wall of the *gall bladder* contained many foam cells but no granuloma. The *pelvic organs*, while grossly normal, showed involvement of the submucosa of the bladder by granuloma and foam cells. Characteristic nodules were present adjacent to the uterine wall but did not involve the muscularis. Many of the autonomic ganglia contained neurons which showed beginning involvement by lipid, but the full blown changes described in the central nervous system were not present. The *larynx* showed only slightly less severe involvement than in the previous case. Several joint cavities were obliterated by fibrosis in which foam cells were prominent, but granuloma formation was much less extensive. The submucosa and epithelium were normal. The *tongue* was rather severely involved. The septa between muscle bundles, especially in the deeper portions, were thickened and fibrotic, while the glands, muscles and epithelium were normal. The *trachea* was minimally involved. The *esophagus*, *thyroid*, and *parathyroid* glands were normal. All the *lymph nodes* were enlarged and fleshy. Microscopically, they showed a depletion of lymphocytes and lipidization of macrophages while the normal architecture was preserved (Fig. 7). The *joints* of this patient showed severe involvement similar to that in the previous case. Large masses of granuloma infiltrated all portions of the synovial membrane (Fig. 8). Pannus was less prominent than in the previous case, but the same matting together of joint, tendon sheath and subcutaneous nodules could be seen, particularly in the fingers, wrists, and on the dorsum of the feet. Microscopically, the reaction was identical to that already described. In the *central nervous system*, the pathological changes were identical with those in the previous patient. The cerebellum, pons, medulla (Fig. 9) and spinal cord were severely involved with lipidization of nearly all the large motor neurons, many of which displayed different stages of degeneration. The smaller neurons also showed lipidization, but to a less spectacular degree. Focal areas of myelin degeneration and gliosis, with gitter cell aggregates, also were common. The Purkinje and Betz cells contained deposits of lipid, but in smaller amounts than the large motor neurons. The cerebral cortex was the least involved portion of the central nervous system.

Case 3

J. D. #376111. This child was a male sibling to the previous patient, born at term, weighing 8 lbs., after an uneventful gestation. During the first two weeks of life he was apparently

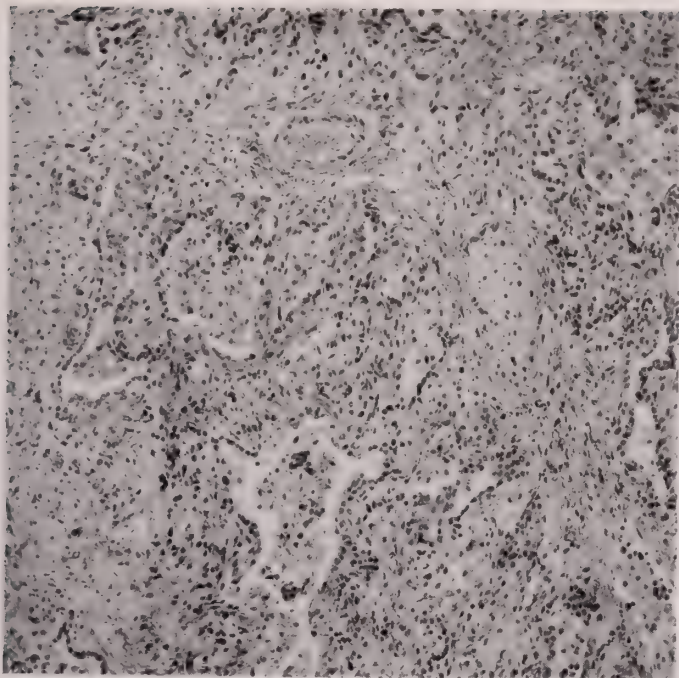


FIG. 6a

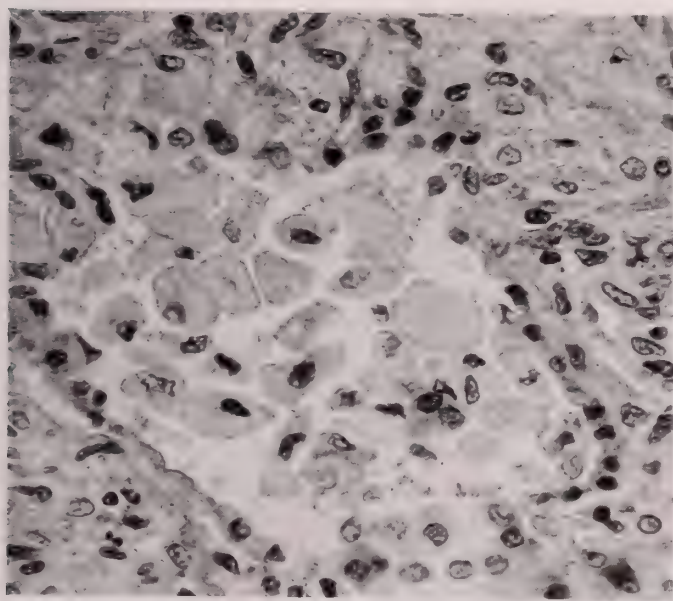


FIG. 6b

FIG. 6 (a)(b). *Case 2*. The lungs show extensive granulomatous involvement of the alveoli and septa. Foam cells are abundant.

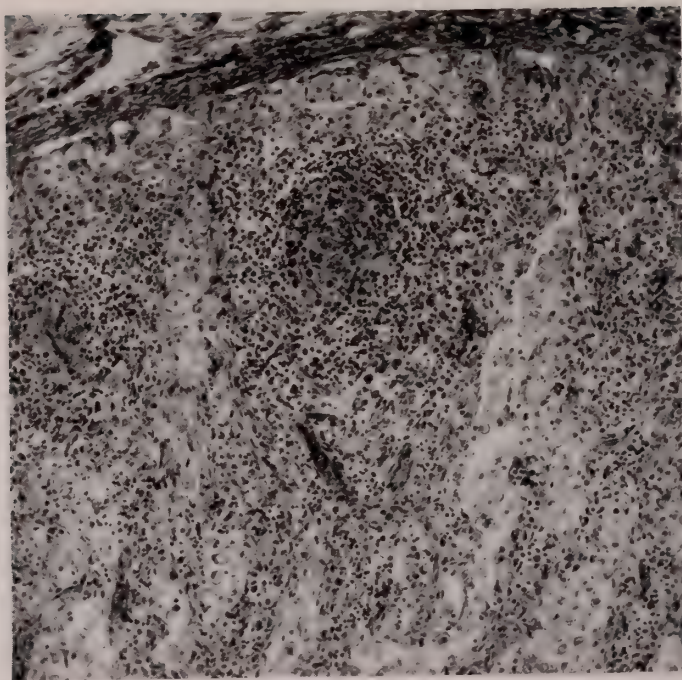


FIG. 7. *Case 2.* Lymph node capsule and primary follicle with many foam cells in stroma of pulp. The structure is preserved.

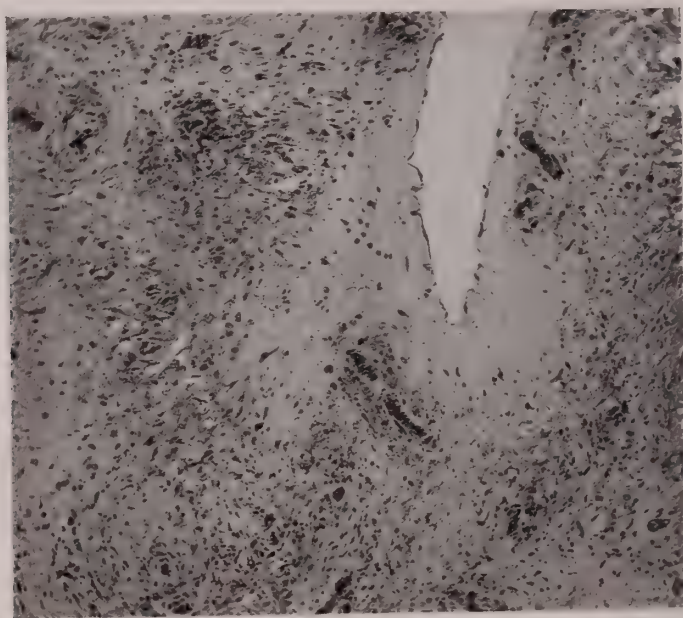


FIG. 8. *Case 2.* Joint cavity with periarticular fibrosis, granuloma and foam cells.

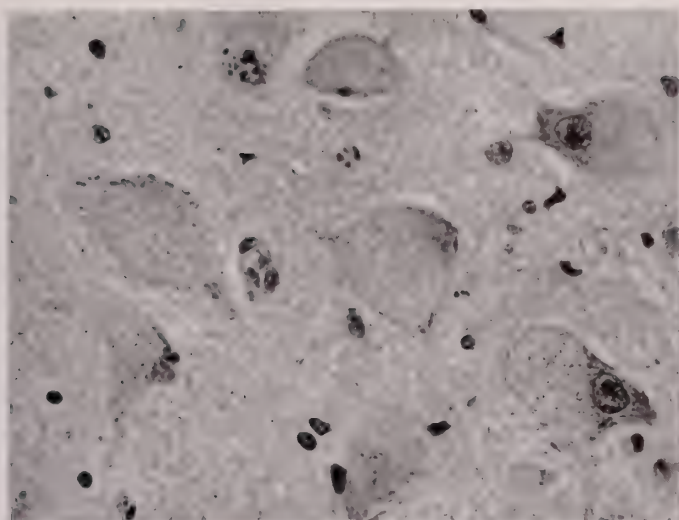


FIG. 9. *Case 2.* The characteristic lipid accumulation in the neurons is evident. These changes were seen in all three cases. Neuronophagia of one cell is evident and gitter cells are also seen.

well. His cry then became hoarse and weak. When he was one month old his mother noticed that he had pain whenever he was picked up, or when he moved. The feet and hands were particularly sensitive. This sensitivity and irritability increased but he was afebrile and his appetite remained good. When he was ten weeks old, swellings were noted on his hands and feet, especially over the joints. He developed a slight cough but had no other respiratory symptoms. One week before hospitalization his mother noticed a forward curvature of the spine and a lump appeared over the lumbar region. All of the joints of the extremities became fairly stiff and moved infrequently.

He was first seen at The Children's Medical Center at the age of three months, weighing 10 lbs., 3 oz. Physical examination revealed an irritable infant whose spontaneous movements were minimal, and whose cry was nearly aphonic. The tongue was thickened. Slight generalized lymph gland enlargement was palpable. Sternal retraction accompanied his respiration, but the lungs were clear to auscultation. The liver was just palpable 1 cm. below the costal margin. The spleen could not be felt. The joints of the extremities were slightly swollen and limited in motion by pain and by flexion contractures. Firm, non-tender nodular swellings were present on the wrists, fingers (Fig. 10), ankles, toes, and over the second lumbar vertebra. There was generalized hyporeflexia.

The positive laboratory findings were as follows. There was mild to severe leucocytosis throughout the course of the disease. The serum cholesterol was 460 mg. per cent on one determination, and 177 mg. per cent on another. The serum total lipids measured 7.7 turbidimetric units (normal 2-5). The fasting serum glucose was 80 mg. per cent but the tolerance curve was markedly elevated (760 mg. per cent at one half hour and 525 mg. per cent after 4 hours). The spinal fluid protein was elevated to 130 mg. per cent and 418 mg. per cent on two determinations. Roentgenograms of the chest and long bones were negative except for the periarticular soft tissue swelling.

The course in the hospital was slowly down-hill. Tonic reflexes became evident. Respiratory difficulty was apparent at first only during feeding and the lungs remained clear to roentgen examination until two weeks before death. Laryngoscopy was negative. At biopsy a nodule and a lymph node showed much fibrosis and foam cell infiltration, but no granuloma. The joint involvement increased progressively (Fig. 10 (a)) and the periarticular and subcutaneous nodules became slightly larger and more numerous. Erosions of bone



FIG. 10 (a)(b). *Case 3*. Progressive change of joint findings is illustrated by the minimal swelling of the interphalangeal joints in Fig. 10 (a) and the marked nodularity of these and other joints of the hands in Fig. 10 (b), taken four months later.

adjacent to the joints appeared on roentgenograms when the infant was five months old, and tibial lesions resembling Wimburger's sign were evident. There was a slow loss of weight and increased dyspnea until death occurred when the child was six and one half months old, at which time he weighed nine and one fourth pounds.

Autopsy Findings. (A52-1. Jan. 2, 1952) Several points of difference from the previous cases were noted but in the generalized distribution of lesions, the pathological picture was quite similar. The *heart*, on its pericardial surface, showed a few white plaques and nodules composed of large mononuclear cells without granuloma formation. The myocardium, endocardium and valves were normal. The *lungs* were heavy and meaty and contained little air. Many nodular thickenings were present in the pleura similar to those in the pericardium (Fig. 11). Histologically, the lung lesion was characterized by diffuse extensive pervasion of the interalveolar septa by mononuclear cells whose cytoplasm was abundant and eosinophilic and without granules or droplets. Degenerated remnants of these cells filled the alveoli and bronchioles. In the *gastrointestinal tract*, the submucosa of the stomach, duodenum, small intestine and colon were infiltrated with varying numbers of mononuclear cells, some of which showed degenerative changes. The *liver*, which was not enlarged or grossly abnormal, histologically showed very thin cords of hepatic cells. Many hepatic cells were necrotic. Others contained faintly staining foamy cytoplasm, similar to that of the adjacent Kupffer cells. The sinusoids were widely dilated. The wall of the *gall bladder* was grossly normal and on section merely showed many foam cells in the submucosa. The *spleen* was not enlarged. Its surface presented a few nodular swellings which were similar to



FIG. 11. *Case 3.* The raised and flat nodules are seen at the borders of the lung substance. Larger plaques and atelectatic consolidation may also be noted.



FIG. 12. *Case 3.* Spleen. A few raised yellow nodules may be seen on the surface of the spleen.

those found on pleural, pericardial parietal and visceral surfaces (Fig. 12). Microscopically, mononuclear cells similar to those in the lung parenchyma were found in moderate numbers scattered in the red and white pulp. The *kidneys, pancreas, adrenal glands* and *testes* were normal. The *bladder* showed marked fibrosis around most of the muscle bundles and in the fibrous tissue, moderate numbers of viable and degenerated macrophages were seen. No inflammation or granuloma were present. Similar fibrosis with mononuclear cell infiltrate occurred in the musculature of the *tongue* and *larynx*. The *lymph nodes* were enlarged. They

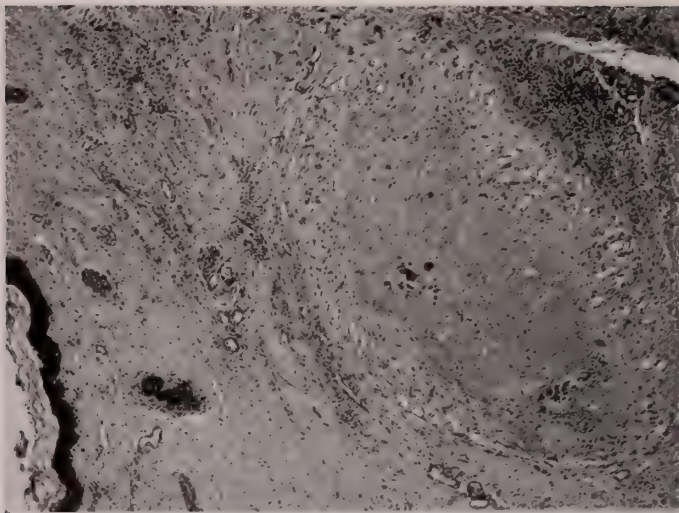


FIG. 13a

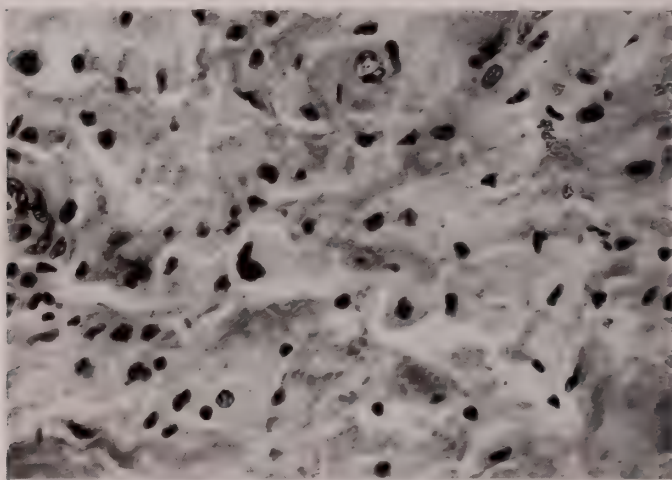


FIG. 13b

FIG. 13 (a)(b). *Case 3*. The subcutaneous nodule shows a necrotic center with a few flecks of calcification. Many foam cells are present.

contained a few lymphocytes and a moderate number of foam cells, some of which were degenerating. The *bones* were grossly normal and microscopically they merely showed the changes of growth arrest and of hypoplasia of the hematopoietic elements of the marrow. The *joints* did not show similar universal involvement as in the previous cases. Of the joints examined, the knees, shoulders, hips, sterno-clavicular and laryngeal joints showed only a slight thickening of the capsular membranes. The wrists and fingers showed a moderate increase in the fibrous tissue of the capsule with some mononuclear infiltration, but only minimal changes in the synovial membrane itself. Near the joints, in the fibrous tissue, nodules similar to those described below were found. All joints showed marked limitation of motion and flexion contractures. In the *skin* and *subcutaneous tissue* sections, the nodules were numerous (Fig. 13). They measured up to 1 cm. in diameter and varied in their

histological configuration. The most common picture was one of numerous macrophages, some of them with foamy cytoplasm, infiltrating fibrous tissue. Other nodules contained masses of degenerated mononuclear cells, with surrounding granulomatous reaction. In some areas, foreign body giant cells were visible, and in a few necrotic portions of fibrous tissue and foam cells, calcification was evident. In the *nervous system* the changes were more advanced than in the previous cases. There was a moderate dilatation of all ventricles and the cerebrospinal fluid was xanthochromic. The brain substance was firmer than usual. On section, the neuronal changes were severe in the pons, medulla, and spinal cord, and moderately severe in the cerebellum. Least involved were the cortex and basal ganglia. The neuronal changes were identical with those previously described. In addition, a few microscopic areas of encephalomalacia and myelomalacia were seen. Areas of myelin degeneration, glial reaction, satellitosis and gutter cell formation were not extensive but could be found easily. A few neurons were seen in the process of neuronophagia. The changes in the autonomic nervous system were much less severe but lipidization of ganglion cells was present in many visceral ganglia. The *pituitary gland* was normal.

CHEMICAL PATHOLOGY

Organs from two of the patients described (E. D. and J. D.) were available for chemical studies. Except for the brain and cerebellum of E. D. which had been fixed in formalin, all tissues had been preserved in the frozen state since the postmortem examinations. Areas that macroscopically showed maximal involvement were carefully dissected out, weighed and used for analysis.

The total lipids were extracted by boiling homogenized tissue samples with chloroform-methanol (2:1). The extract was taken to dryness *in vacuo*, redissolved in chloroform-methanol and made up to suitable volumes. Lipid-phosphorus was determined according to Sperry (2), non-saponifiable lipid phosphorus according to Brante's modification (3) of the Schmidt-Thannhauser procedure (4), and expressed as sphingo-myelin. Lipid hexose was estimated by a modification of the method of Brand and Sperry (5), using the adaptation of the Folin and Malmros (6) procedure for determination of the reducing value. Cholesterol was determined by a modification of the Schoenheimer-Sperry method (7). The iodine number was determined with a modified Hübl's reagent. The result of the analyses have been indicated in Tables I and II.

Since the lipid hexose values were unusually high in both cases and because no cerebrosides could be isolated from the lipid extracts of the livers and lungs, it appeared probable that we were dealing with an unknown type of lipid containing polysaccharide residue or residues.

As a result of many pilot experiments, the following two procedures were found to lend themselves best to the isolation of this material which was found to be lipo-glycoprotein in nature as indicated by the following studies.

Method I

The tissue was finely minced and extracted with boiling 2:1 mixture of chloroform-methanol (20 mls. gm. fresh tissue). The lipid extract was filtered on a Buchner and the clear filtrate cooled to room temperature. To 500 mls. of extract, 150 mls. of water were added and the mixture shaken intermittently but vigorously for four hours, and then left twenty-four hours in the cold room (+2°C). The mixture separated into three layers at the end of this period.

TABLE I

Organs	Total Lipid as % Fresh Weight	Total Phosphatide as % Total Lipid	Unsaponifiable Phosphatide (Sphingomyelin) as % Phosphatide	Lipid Hexose (Glucose Equiv.) as % Total Lipid	Iodine Number	Cholesterol as % of Total Lipid	Lipoglycoprotein as % Total Lipid (by Isolation)
Kidney.....	3.38	31.96	18.3	2.82	40.85	—	
Spleen.....	6.10	24.64	18.5	2.14	36.06	—	
Heart.....	4.05	40.02	14.6	4.20	46.24	—	8.0
Liver.....	9.35	35.45	Traces	5.62	54.60	6.7	15.0
Lung.....	4.001	35.75	16.5	7.12	37.17	5.7	20.4
Bowel (Ileum).....	4.60	15.72	—	—	34.33	—	
Brain (Formalin).....	4.85	55.60	—	—	45.86	16.3	
Cerebellum (Formalin).....	4.88	57.60	—	—	42.97	—	

TABLE II

Organs	Total Lipid as % Fresh Weight	Total Phosphatide as % Total Lipid	Unsaponifiable Phosphatide as % Total Phosphatide	Lipid Hexose (Glucose Equiv.) as % Total Lipid	Cholesterol as % of Total Lipid	Iodine Number	Lipoglycoproteins % Total Lipid (by Isolation)
Kidney.....	1.59	37.05	19.6	5.05	6.75	54.2	—
Heart.....	1.12	43.5	28.7	5.52	5.21	38.4	—
Liver.....	6.15	35.4	13.6	6.62	4.95	60.6	29.9
Lung.....	5.41	45.8	17.9	3.87	5.11	71.2	19.6
Spleen.....	3.90	36.1	24.1	3.29	8.30	58.6	—
Knee-Joint periarticular tissue.....	3.20	19.7	86.6	2.50	Traces	—	—

These were mixed with shaking and the mixture was centrifuged at 3000 rpm. for 20 minutes in 100 ml. centrifuge tubes. The resulting tightly-packed middle layer was separated by siphoning off the top and bottom layers, and dialyzed twenty-four hours against distilled water. The middle layer was then suspended in 500 mls. of water and partitioned against chloroform. The top aqueous layer was carefully separated and lyophilized. The final product consisted of the lipo-glyco-protein fraction.

Method II

The tissue was extracted with the chloroform-methanol mixture as described in Method I. *In vacuo*, 500 ml. of lipid extract was reduced to 50 mls. To this, 50 mls. of water were added, shaken for two hours, and centrifuged 20 minutes at 3000 rpm. The ensuing top layer was siphoned off (layer a) and another 50 mls. of water added to the bottom layer. After shaking for another two hours this mixture was again centrifuged, and this time the top and middle (inter-phase) layers were siphoned off (layer b). Layers (a) and (b) were combined, dialyzed against distilled water and taken to dryness *in vacuo* at room temperature. The fractions thus obtained were identical with those obtained by Method I.

Chemical Composition of Lipoglycoproteins

The lipids were extracted from the fractions by boiling the dry material for 12 hours with chloroform-methanol and subsequently for twelve hours with absolute ethanol. The chloroform-methanol and ethanol extracts were combined and taken to dryness. The lipids thus obtained accounted for 24.6 per cent of the total complex. Fatty acids accounted for 42.2 per cent of the total lipid, and neutral triglycerides for 7.8 per cent of the total lipids (calculated from total glycerol-minus saponifiable phosphatide glycerol). Phosphatides were found to contribute 49.4 per cent of the total lipid moiety. Unsaponifiable phosphatides accounted for 82.0 per cent of the total phosphatides and then the bulk of the phosphatide moiety was presumably sphingomyelin. Paper partition chromatography of the lipid moiety (8) using ninhydrin as the detecting reagent indicated phosphatidyl-ethanolamine to be absent and phosphatidyl-serine present in traces.

The residual material after removal of the lipid-moiety was dissolved in water by the addition of a few drops of alkali (pH 7.5). An aliquot of this solution was treated with two volumes of 2 N-NaOH at 80° for ten minutes. The protein was precipitated by cooling the solution, neutralizing with hydrochloric acid and adding of 2 volumes of 10 per cent trichloroacetic acid. The polysaccharide moiety was precipitated from the trichloroacetic acid supernatant by addition of 2 volumes of 95 per cent ethanol, washed with absolute ethanol and dried *in vacuo*. The polysaccharide moiety thus obtained accounted for 32.2 per cent of the total lipo-glycoprotein complex. After acid hydrolysis, 64 per cent of the polysaccharide was found to consist of reducing substances (expressed as glucose equivalents).

The protein moiety of the complex obtained by trichloroacetic acid precipitation, as described above, was hydrolyzed in sealed test tubes with 6 N HCl at 110°C for ten hours. After the acid had been removed by taking the sample repeatedly to dryness *in vacuo*, the hydrolyzate was chromatographed on paper, using phenol-water and butanol-ethanol-acetic acid-water for two dimensional runs. The following amino acids were detected: alanine, glycine, cystine, serine, threonine, aspartic acid, glutamic acid, tyrosine, arginine, phenylalanine, (?) methionine, leucine (plus isoleucine ?) and histidine (?). Alkaline hydrolysis in the presence of 5 per cent stannous chloride failed to reveal the presence of tryptophane.

That the protein moiety consisted of a mixture of proteins (or polypeptides) was revealed when an aqueous solution of lipid-free, polysaccharide-free protein moiety was subjected to paper electrophoresis. Although the processes used in the extraction of the lipid and dissociation of the polysaccharide moieties were drastic enough to have "denatured" the protein residue, they were not sufficient to cause hydrolysis. Thus there were no free amino acids prior to hydrolysis, and the fractionation by electrophoresis on paper yielded constant results for three different preparations obtained from the liver and lung of the two cases. The resulting separation is given in Table III, showing the presence of six definite, well-demarcated components, with only one of them, however, of suffi-

TABLE III

Paper electrophoresis of protein moiety

4 hrs. at 20 volts/cm potential gradient 0.1M diethylbarbiturate buffer pH: 8.6

ANODE←	→CATHODE
10.0 mm. Ninhydrin + Bromphenol Blue-Sublimate +	4.5 mm. (Ninhydrin: Green-Gray)
37.0 mm. Ninhydrin +	13.5 mm. (Ninhydrin: Red)
	28.0 mm. (Ninhydrin: Purple L)
	55.0 mm. (Ninhydrin: Purple)

cient size to react with bromphenol blue sublimate reagent. Presumably the other five components have to be ascribed to larger polypeptides.

From consideration of the above, it becomes clear that the high lipid-hexose values for the lipid analyses of the organs of E. D. and J. D. are due to the presence of large amounts (up to 24 per cent of total lipid) of this lipo-glycoprotein fraction in the lipid extracts. The unusual character, composition and physical properties of this complex appear to be the chemically abnormal counterpart of the pathological entity here described. As such, it presents a hitherto undescribed "storage substance", the pathogenesis of which remains obscure. Because of the large amounts of lipids normally present, neither the analyses nor the isolation procedures here described lent themselves to the detection of the lipo-glycoprotein fraction in the lipid extracts of the brains of these cases. However, since there was no doubt regarding the central nervous system involvement on histological examination of various areas, as described previously, it was reasonable to resort to histochemical demonstration of the material in involved neurons.

Because of the highly polysaccharide content of the complex, the periodic acid-fuchsin staining was chosen, as this would undoubtedly demonstrate material of polyglycol nature if the latter were to be present in significant concentration in the nerve cells. This assumption proved justified when the cytoplasm of involved nerve cells was found to be stained diffusely red. The staining was somewhat granular in appearance and did not show the perinuclear clear zone that is observed in Tay-Sachs disease, where the storage material (ganglioside) (9) also possesses a high content of sugar residues. The recently developed phosphomolybdic acid stain (10) for choline containing phosphatides was negative, and thus it must be assumed that the sphingomyelin is present in a "masked" form.

DISCUSSION

This new syndrome, for which the name of lipogranulomatosis is employed (1), presented a rather uniform clinical picture which was easily recognizable once the first case had been studied. The onset, soon after birth, consisted characteristically of sensitivity and swelling of the extremities, accompanied by a hoarse weak cry. The progress of the disease was marked by chronic, progressive, severe and generalized involvement of joints, by the appearance of nodules in

the subcutaneous and periarticular tissues, by increasing dysphonia because of fixation of the laryngeal cartilage, and finally by dyspnea when pulmonary infiltration supervened. The alternating febrile and afebrile periods during the first stages of the disease should be noted. One other constant physical finding was a slight enlargement of the lymph nodes; the spleen and liver were not enlarged.

The characteristic course of the disease in our three patients was interesting with respect to the tissues successively involved and also to problems in differential diagnosis. The extremities and the larynx were the first areas to show characteristic lesions, but systemic symptoms of irritability, febrile episodes, and poor weight gain also were evident from the onset. At that stage of the disease, the diffuse swelling and hyperesthesia of the extremities called attention to the skin lesions, and concealed those of the joints. As the skin swelling subsided, the articular involvement became obvious and then it was recognized that the hoarseness was due to joint involvement in the larynx. The problem became one of differential diagnosis of a generalized disease involving lesions of skin and joints and throughout the disease, until signs of visceral involvement overshadowed them, these lesions remained outstanding.

The skin lesions, which at first consisted of generalized swelling of the skin of the extremities, soon changed into nodular thickenings near most joints and tendon sheaths and on the chest, abdomen and occiput. One patient had a brown, desquamating, and, later, crusting dermatitis of the hands and feet, but the other two did not. The diffuse swellings in the extremities subsided slowly over a period of weeks, leaving slight subdermal nodularities, and these nodules tended to grow slightly and to multiply during the course of the disease. Only a few nodules shrank as the disease progressed, and an occasional nodule disappeared.

The articular lesions in these patients were undoubtedly among the first manifestations of the disease. Two of three patients, seen at this hospital early in the disease, had had articular involvement for two months or more, and their lesions were severe, even on initial examination. The third patient, concerning whom the initial phases of the disease were well recorded at another hospital², also manifested similar restriction of joint motion early in the disease. It is difficult to recognize the earliest degrees of joint involvement in irritable infants, whose extremities are sensitive. Furthermore, hoarseness, when caused by immobility of the laryngeal cartilages, must represent a rather advanced state of joint involvement, since it is extremely rare in other, less severe, types of generalized arthropathy. These considerations point to an insidious and very early involvement of joints, perhaps in the immediate neonatal period, perhaps even during fetal life.

The first sign of visceral involvement occurred when the lesions of the skin and joints were moderately advanced. The exact onset of involvement of the central nervous system was difficult to ascertain. Some observers, in retrospect,

² We are indebted to the Harriet Lane Home and Dr. Harriet G. Guild for this information.

considered the hyperesthesia and immobility as possible evidence of neuronal involvement but the cutaneous and articular lesions seemed adequate reasons for the symptoms. While pathologic reflexes were evident in two patients late in the disease (ED and JD), and blindness in one (ED), other clinical evidences of a neurological lesion were difficult to evaluate. The retardation in development seen in these patients was to be expected with a disease of such severity and chronicity in infants. Several examiners considered the extreme debility, combined with the dysfunction of joints, to be an adequate cause, during the advanced stages of the disease, for the lack of response to stimuli, the absence of some reflexes, and the loss of motor function. They did not attribute these findings to paralysis and anesthesia due to lesions in the central nervous system. These aspects of the neurological findings are mentioned to emphasize the difficulty in clinical evaluation of the central nervous system symptomatology in the presence of such widespread disease, even though on postmortem examination, ample evidence for such involvement was obtained.

The onset of visceral involvement in organs other than the central nervous system became apparent very late in the disease. All three patients had pulmonary lesions terminally, but roentgenograms revealed that in each case, the lesions had their onset five months or more after the beginning of the disease. Another late lesion, which appeared secondary to the original process, was the juxta-articular destructive lesion of bone. This was rather distinctive radiologically but did not cause additional symptoms. They were present in all three patients and occurred most characteristically at the sigmoid notch of the ulna. The changes in the bones at postmortem were found to be caused by invasion by nodular infiltrate from the involved adjacent joints.

A comparison of the pathology of the joints and subcutaneous nodules at autopsy in the three cases was of interest. In the last patient, (JD) the joints were not severely infiltrated, and granuloma did not occur in the joint capsules. The main reaction was one of fibrosis. The macrophages, while numerous, did not usually contain the foamy cytoplasm seen in the other two cases. The nodules also were not as large and only occasionally manifested a granulomatous component, and this usually in relation to necrotic masses of macrophages. By way of contrast, the first patient (JB) presented a pathological picture in the joints and nodules in which massive involvement by granuloma predominated, although large numbers of foam cells were interspersed in the lesions. The second patient (ED) represented an intermediate stage in the composition of joint and nodular lesions. This evidence points to the probability that, in the genesis of the systemic lesions, lipidization of macrophages was a late phenomenon, and granuloma formation an even later reaction. The earliest reaction which could be discerned was one of simple fibrosis and accumulation of non-foamy macrophages. The pathological picture in the lung tends to bear out these conclusions. Pulmonary involvement in all three patients was extensive, but in the third patient, JD, it was of short duration as judged by roentgenograms. The pathological picture was one of infiltration of the parenchyma and alveoli by macrophages, most of which were not foam cells. No granuloma was

seen. Despite this variation in the numbers of foam cells in the lesions of ED and JD, the content of stored lipid in the two cases was similar.

It is of interest to note that the third patient, JD, showed more extensive visceral involvement than the other two. In this patient, the metabolism of glucose, as measured by the glucose tolerance test, was abnormal and at autopsy the liver involvement was severe. The wall of the gastrointestinal tract of this patient also was diffusely infiltrated. The early death of this patient, compared to the others, may have been partly caused by the metabolic disturbances secondary to these infiltrates.

Because of the bizarre joint symptoms and the subcutaneous nodules, the initial impression of many observers of these cases was that of rheumatoid arthritis. The age of onset of the disease made this diagnosis unlikely, since rheumatoid arthritis has not been reported in the immediate neonatal period. A biopsy of a lymph node and subcutaneous nodule revealed the collection of foam cells and allowed the diagnosis of lipogranulomatosis to be made.

The morphological alterations in the neurons, which were an outstanding feature of these cases, are noteworthy not only for their widespread incidence, but for their similarity to those found in a small group of diseases, all of which are rare. These diseases—Niemann-Pick disease, Tay-Sachs disease (amaurotic family idiocy) and Hurler-Pfaundler disease (gargoylism) are usually classified either as heredo-degenerative diseases of the central nervous system or as disturbances of lipid storage or metabolism. Lipogranulomatosis may be distinguished from the diseases mentioned by the type of generalized systemic involvement. The neurological lesions are essentially indistinguishable in this group of diseases, particularly with reference to the morphological changes in the neurons and the extreme variability encountered in the localization of lesions. No correlation has been found between the site of involvement of the nervous system in these diseases and the type of visceral or systemic involvement, and no such correlation could be established in the present series of cases. Some significance may attach to the three cases described as still another instance of differential systemic changes associated with the same type of neuronal pathology. It, therefore, becomes less likely that the same or similar metabolic or genetic factors are operative in these diseases if the lesion of nerve cells is considered the primary one.

The systemic lesions described in the three patients in this report distinguish this syndrome from the other lipoidoses. The extensive enlargement of the liver and spleen, which is a distinctive feature of Niemann-Pick disease, was not present. While a lesion of the liver in the last case (JD) could be interpreted as the beginning of the replacement of hepatic tissue by foam cells, the absence of coordinate splenic lesions, and the demonstration that the lipid present was not sphingomyelin provided adequate diagnostic differentiation.

Gaucher's disease, another of the lipoidoses, bears no similarity either clinically or pathologically to lipogranulomatosis, and is mentioned merely for completeness. Passing reference should also be made to the group of diseases consisting of Letterer-Siwe disease, the Hand-Schüller-Christian syndrome, and

eosinophilic granuloma, since these too are usually discussed in conjunction with the lipoidoses and, in addition, are the only ones where a foam cell component is found in a granulomatous process. While differential diagnosis between lipogranulomatosis and this group presents no difficulties either clinically or pathologically because of the variance in the localization and course of the lesions, comparison is necessary to demonstrate that lipogranulomatosis should not be considered another member of this disease group because of the foam-cell-granuloma complex. In this connection, it should be pointed out that the eosinophilic leucocyte so commonly found in the granulomas of the group in question was not seen in the three patients under discussion, that the sequences of granuloma formation in lipogranulomatosis preferentially localizes near joints and subcutaneously, while that of this disease group seeks out the bones, liver, spleen and lymph nodes, and finally, that the lipids involved are not related.

The pathogenesis of lipogranulomatosis is obscure. While all of the three infants' disease began with an upper respiratory infection, no infectious etiology could be established, or seems likely. The occurrence of the same, rare disease in two siblings certainly raises the possibility of a familial entity but this remains speculative in the absence of any other cases in either family. The generalized accumulation of large quantities of lipid material constitute a valid criterion for inclusion of this syndrome among the lipoidoses, yet analysis of the material tends to differentiate it from the other members of this group.

With respect to its composition, this storage material bears close relationship to the storage substance of gargoylism (9) where the material, although different in its anatomical distribution, has a large polysaccharide residue forming a complex with a polypeptide. The chemical similarity is also paralleled by the same type of central nervous system involvement with periodic acid-fuchsin positive material filling a wide variety of nerve cell bodies. The lipo-glyco-peptides here presented are, however, distinct in their remarkable property of being soluble in organic solvents preferentially. It would appear that this property has to be ascribed to the non-polar nature of the lipid residue. Yet the fact that they will orient themselves at the interphase of an organic solvent-water system also suggests that they possess some hydrophilic groups at the surface of the giant complex to permit such antivalence.

From consideration of the above, it becomes clear that the high lipid-hexose values for the lipid analyses of the organs of ED and JD are due to the presence of large amounts (up to 26 per cent of total lipid) of this lipo-glycoprotein fraction in the lipid extracts. The unusual character, composition and physical properties of this complex appear to be the chemically abnormal counterpart of the pathological entity here described. As such, it presents a hitherto undescribed "storage substance", the pathogenesis of which remains obscure.

ACKNOWLEDGEMENT

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SOME UNCOMMON FORMS OF CEREBRAL VASCULAR DISEASE

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Abnormalities in the cerebral blood vessels constitute the most common forms of cerebral disease. These abnormal vessels occasionally rupture causing hemorrhage, but in most cases, their lumens are narrowed or occluded, thereby decreasing blood flow and causing ischemia and often infarction of cerebral tissues. In some cases, vessels which are themselves essentially normal may be ruptured, as in trauma, may be narrowed as a result of compression by adjacent structures, or may be occluded by emboli.

In most instances, arteriosclerotic and hypertensive processes are directly involved in producing the vascular abnormalities. There is in addition a heterogeneous group of diseases in which the vascular abnormalities are of a less common type. It is the purpose of this paper to review our experiences with some of these uncommon forms of cerebral vascular disease.

We consider it a privilege to be permitted to include this review in a volume dedicated to Dr. Paul Klemperer.

ANEURYSM

Most aneurysms of the cerebral arteries are of the saccular, "berry" or "congenital" type. These are saccular excrescences, generally 0.3 to 1 cm. in diameter, located most often near the point of branching of a vessel in the anterior portion of the circle of Willis, but they may be found on any major vessel at the base of the brain. They are not infrequently multiple. They are most commonly observed in persons in the third or fourth decade of life (1), but may be seen in youth and even in childhood. The aneurysm is generally composed of dense collagenous tissue; smooth muscle and elastic tissues are absent, or are present only as small irregular fragments.

These aneurysms are considered congenital, not in the sense of being present at birth, but in the sense that they result from an acquired injury superimposed upon a congenital defect in the vessel wall. The nature of the congenital defect is not entirely clear, being thought by some to be the persistence of a short segment of an abortive branch when the remainder of the embryonic capillary plexus is absorbed (2). Others implicate the absence of the media at the aneurysmal site (3, 4). These medial defects in the cerebral arteries are so common that their

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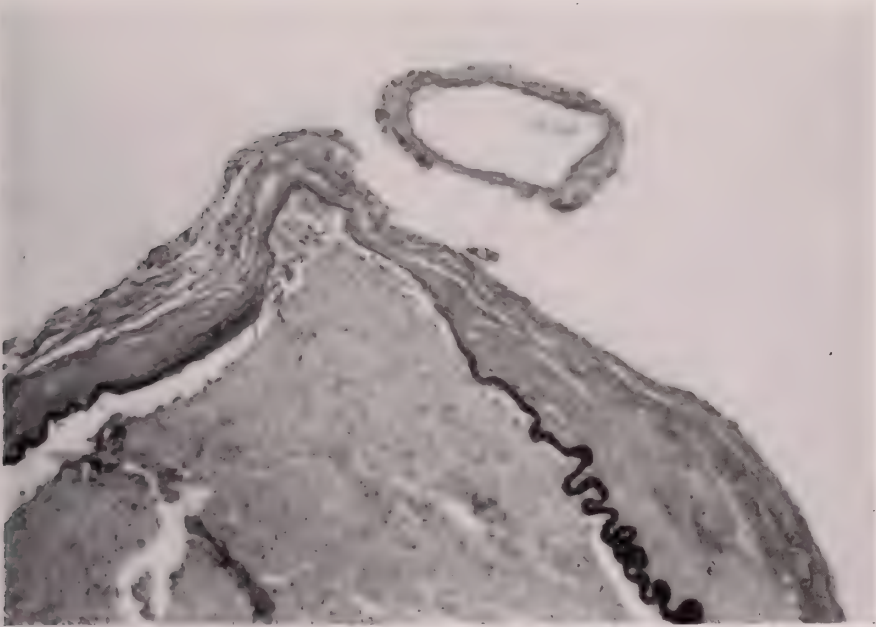


FIG. 1. Defect in cerebral artery at or near a point of branching in individual without aneurysm. The media is absent, and the elastica is markedly thinned over a broad zone. Elastica Van Gieson, $\times 350$.

significance has come to be discounted (5, 6), especially since similar defects are found in vessels in other organs in which such saccular aneurysms are not observed. Defects in the elastic membrane may be of greater significance, although data are not adequate to indicate clearly whether such defects are congenital or acquired (7). When one considers that the walls of cerebral arteries are normally much thinner than vessels of like caliber in other organs, and that elastic fibers are present only in the internal elastic membrane, it will be recognized that the medial and elastic defects (Fig. 1) mentioned are sites of marked weakness. The coincidental finding of coarctation of the aorta or polycystic kidneys has been noted with significant frequency. This may support the interpretation that these aneurysms are congenital, but may also reflect the role of coexistent hypertension as noted in the next paragraph.

In some instances, such as those noted in children, these defects may be sufficiently severe in themselves so that aneurysms develop, rupture and cause hemorrhage. In most instances, it may require an additional acquired local injury, possibly wear and tear, aging, arteriosclerosis and/or hypertension to cause the outpocketing and rupture. Some degree of arteriosclerosis is almost always present in the aneurysm as is true in most individuals in the predominating age group. Hypertension is even more clearly significant, perhaps by increasing the severity of sclerotic changes, possibly by increasing the incidence of aneurysm formation, and certainly by increasing the likelihood of rupture, so that such aneurysms cannot escape attention. Some do not accept the concept of an antecedent congenital

defect, believing that acquired alterations in the wall of a cerebral artery may result in such saccular aneurysm because of the unique character of the walls of these vessels (6).

In most cases, aneurysms cause cerebral injury by rupture, causing hemorrhage into the subarachnoid space and/or into the brain substance. Hemorrhage into the closed cranial cavity of fixed volume must necessarily be disastrous because of the concomitant pressure upon vital cerebral tissues. Not infrequently, the aneurysm itself or the hemorrhage caused by its rupture may occlude the vessels on which it is located inducing infarction of portions of the tissues supplied by the occluded vessel. These infarcted tissues may lie at a considerable distance from the site of direct injury by the aneurysm. Rarely, the aneurysm may grow quite large, and slowly compress adjacent tissues. Occasionally, the total mass of hemorrhage and edematous infarcted tissue may cause the anterior portion of the hippocampal gyrus to herniate beneath the free edge of the tentorium, compressing the brain stem and more significantly the veins and possibly the arteries related to it and cause multiple hemorrhages into the brain stem, like those seen so commonly in cerebral neoplasms. In one instance, it was observed that a posterior cerebral artery was compressed by such a mechanism so that infarction of the occipital lobe had resulted in a patient in whom an aneurysm of the anterior communicating artery had ruptured (8).

In some cases of cerebral arteriosclerosis, the basilar artery may become tortuous and elongated, and instead of being narrowed, may become appreciably dilated. The term "arteriosclerotic aneurysm" is applied to such structures, although these are of limited clinical significance. Occasionally, a large aneurysm is noted, saccular in character, in which arteriosclerotic changes are unusually marked. It is not clear whether such aneurysms are essentially arteriosclerotic in character, or are atypical congenital aneurysms showing an unusually severe arteriosclerotic component. Rupture is infrequently observed.

In some infectious processes, particularly the bacterial endocarditides, emboli containing pathogenic micro-organisms, may lodge in a vessel inducing a local inflammatory reaction to which the term "mycotic aneurysm" is applied. In our experience, the vessel walls are more often destroyed than aneurysmally dilated but such saccular dilatations have been frequently observed by others (9).

OTHER VASCULAR AND ANGIOMATOUS MALFORMATIONS

Anomalies of the arteries at the base of the brain are very common. These may include supernumerary vessels, absent vessels and vessels with abnormal distribution or caliber. Among the more common major anomalies, are those in which a posterior cerebral artery derives its major blood supply from the internal carotid artery through a large posterior communicating vessel, and those in which an anterior cerebral artery is supplied largely from the opposite side through a large anterior communicating artery. In our experience, such abnormalities are not associated with cerebral lesions, and this was true in as marked an abnormality as the congenital absence of one internal carotid artery. These abnormalities are of clinical significance only in special circumstances, it being

obviously unwise to ligate the remaining internal carotid artery in the case just cited.

Angiomatous malformations may be classified as capillary, venous or arterio-venous. The latter two types are readily differentiated at the operating table by the presence of arterial blood in the vascular channels in the arterio-venous aneurysms. Histologically, these two types are more difficult to distinguish since both are composed of distorted, thick walled fibrotic channels in which elastic fibers are irregularly distributed. Some believe that an angioma initially venous in character may gain arterial connections becoming arterio-venous in type (10). Clinical signs and symptoms are often delayed until the second or third decade of life (11). In some cases, compression of the neural tissues within or adjacent to the congery of abnormal vessels may result in repeated convulsive episodes. The malformation may also bleed into the neural tissues resulting in more serious clinical findings. It is not clear if thrombosis is frequent or generally causes injury. Such was not observed in our cases.

INFECTIOUS ARTERITIS: BACTERIAL

Arterial changes are not generally observed in acute suppurative leptomenigitis, except in rare instances in which an acute inflammation of the vessel wall is noted as part of a very severe fulminating infection. The neural parenchyma is more apt to be the site of a suppurative encephalitis than of infarction. Others report a greater incidence of vascular disease (12). The effect of infected emboli on arterial walls has already been noted, c.f. "mycotic aneurysm".

The advent of chemotherapy has resulted in the cure of many patients with tuberculous meningitis, while in many others the course of the disease has been considerably prolonged before a fatal termination. As a result, the active inflammatory changes in the vessel wall formerly noted are now observed to continue to a severe endarterial fibrosis and a marked decrease in the size of the lumen. The intima, which is normally very thin, may be replaced by a delicate loose-meshed, poorly cellular, collagenous connective tissue quite different from that seen in arteriosclerotic processes, and this forms large eccentric or wide concentric plaques leaving a very greatly reduced lumen (13-15). There may be little or no infiltration of this intimal connective tissue by inflammatory cells. The internal elastic membrane and the media often appear intact. The adventitial connective tissues are fibrotic and infiltrated by inflammatory mononuclear cells, this process being continuous with the involved leptomeningeal tissues. These changes are observed in those local areas in which the leptomeningeal inflammation and fibrosis is most severe. The arterial change must, of necessity, be related to the inflammatory process, despite the absence of obvious inflammation in the media and in the fibrotic intimal plaques. It has been suggested that it may be the direct result of the effect of a bacterial "toxin" (14). However, if one assumes that one segment of an artery is stenotic due directly to inflammation, the end-arterial connective tissue in other segments may conceivably be produced by the same mechanisms that are involved in the somewhat similar changes noted in arteries in which blood flow is markedly reduced, such as in the proximal stump of an amputated limb, or in senile uteri.

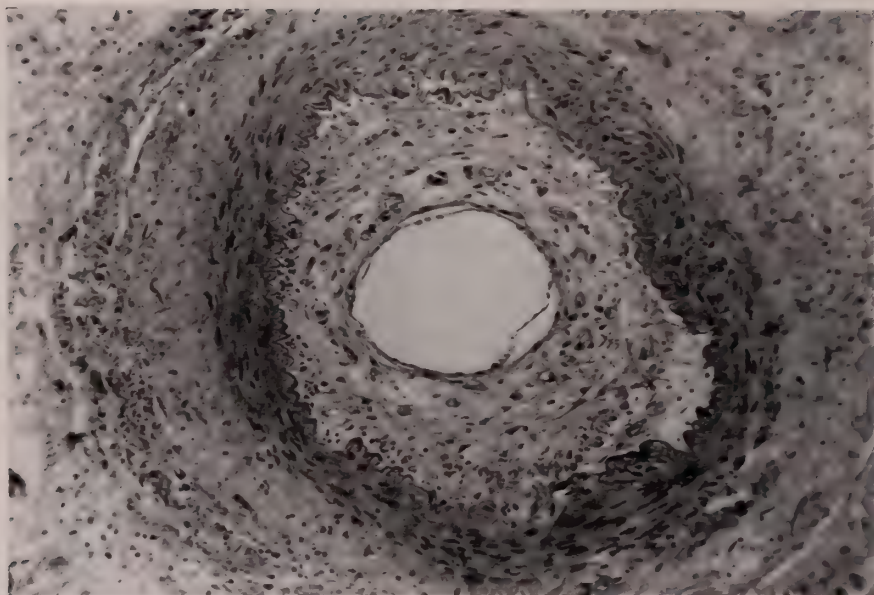


FIG. 2. Cerebral artery in chronic pneumococcal leptomeningitis. The intima is markedly thickened; the elastica and media are relatively well preserved. Hematoxylin and eosin, $\times 130$.

In any case, the circulatory defect resulting from this arterial change may result in ischemic infarction of neural tissues. This has been observed in the spinal cord (16) and in the brain (15) in which the infarcts are more commonly observed near the base, reflecting the site of most severe leptomeningeal and concomitant arterial change. Such parenchymal infarcts are far more common than direct tuberculosis involvement of the parenchyma (tuberculous encephalitis or tubercle formation), and clinical changes indicative of parenchymal injury are more properly attributable to infarction.

An almost identical type of arterial injury (Fig. 2) with cerebral infarction may occur in refractory cases of pneumococcal meningitis in which a chronic leptomeningitis with fibrosis had occurred (12). The arterial change under consideration would appear to be the result, direct or indirect, of chronic inflammation rather than a specific alteration in tuberculous infection.

INFECTIOUS ARTERITIS: FUNGAL

No vascular changes were observed in cases of chronic cryptococcal meningo-encephalitis and this may be related to the minimal degree of inflammatory reaction present in many of these cases. In cases in which the leptomeningeal inflammation is severe, arterial changes like those present in chronic bacterial leptomeningitis may be observed (17). In cryptococcosis many of the perivascular spaces are cystically dilated and filled with organisms, so that the passage of materials between the vessels and the tissues must be impaired.

Other fungal infections are quite rare although we have seen one instance in

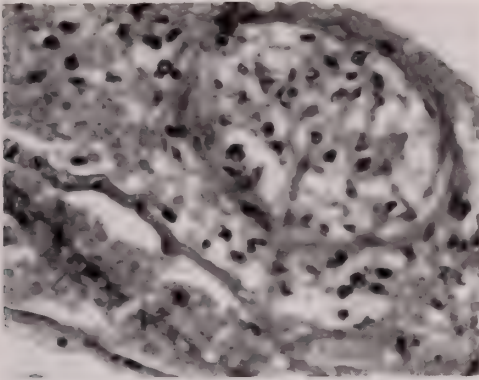


FIG. 3. Leptomeningeal vessel in *Candida albicans* meningitis. A hypha is passing through the vessel wall, and the vessel is occluded by the inflammatory process. Hematoxylin and eosin, $\times 400$.

which a fungus, presumably *Candida albicans*, caused a leptomeningitis and arteritis. The patient had lupus erythematosus, and was treated for an extended period with cortisone and a variety of antibiotics. She developed a fungal infection of the pharynx and lungs, as well as the brain. *Candida albicans* had been cultured from the urine. The morphology of the fungus in post mortem sections, i.e. branched septate hyphae, is consistent with this diagnosis. The inflammatory process consisted of irregular, moderately large patches of leptomeningeal infiltration by many large mononuclear cells, a few polymorphonuclear leucocytes, and a few lymphocytes and associated with the deposition of moderate numbers of collagen fibers. Within such zones the walls and lumens of the intermediate and small arteries and veins were infiltrated by inflammatory cells and fibers of like character, often resulting in occlusion. The adjacent neural parenchyma was infarcted and the inflammatory infiltrate was observed to pass into these necrotic tissues for short distances. There were two zones of necrosis, each averaging about 5 cm. in diameter. Grossly they differed from ordinary cerebral infarcts in presenting a peculiar grey discoloration. Microscopically, they resembled the usual ischemic infarct, except for the presence of more than the average number of polymorphonuclear leucocytes in some areas. Branching septate hyphae were present in small numbers in some portions of the infarct, in the leptomeninges and in some of the affected vessels (Fig. 3).

In *candida albicans* meningitis, both arteritis (18) and cerebral infarction (19, 20) have been reported, while arterial changes not accompanied by cerebral infarction, were described in *Allescheria boydii* meningitis (21).

NONINFECTIOUS ARTERITIS

We have not seen cases of cerebral involvement in classical periarteritis nodosa, although this has been described (22-24). The frequently observed peripheral neuropathy is the result of arterial involvement (22).

We have seen two cases of arterial involvement of obscure character, characterized by a granulomatous alteration in the arterial walls, to which the de-

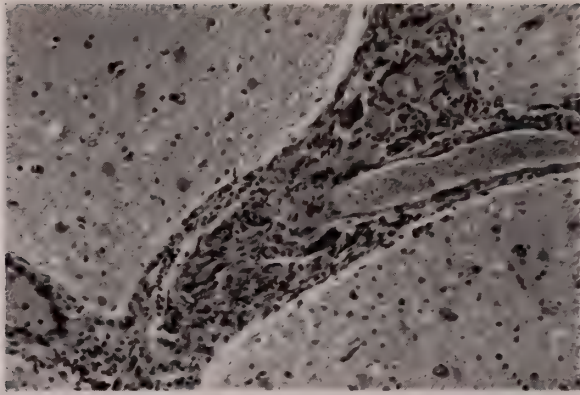


FIG. 4. Granulomatous involvement of wall of intracerebral artery, in "granulomatous angiitis". Hematoxylin and eosin, $\times 130$.

scriptive term, "granulomatous angiitis", may be properly applied. In each case the clinical features were primarily neurological in character and death occurred in a few months due to infarction of cerebral tissues. In one case there was fairly extensive involvement of the intima of the aorta and pulmonic arteries and of the walls of some coronary vessels, and granulomas not obviously related to vessels were present in the spleen, lymph nodes and liver. In the other case, no extracerebral involvement was noted. In the larger cerebral arteries, such as the middle cerebral artery, the granulomatous change was limited to the intima which was usually transformed into an eccentric plaque composed of reticulin and collagen fibers, large mononuclear cells of diverse character, and multinucleated giant cells of foreign body and Langhan's type. In some of these instances, the remainder of the artery appeared entirely normal. In the smaller arteries (Fig. 4) the adventitia as well as the intima were the sites of such granulomas. The media was sometimes normal, sometimes thin and in some cases lost, so that the granulomatous tissue comprised the entire thickness of the wall. The smaller intraparenchymal arteries were often severely involved, so that large granulomas were observed within which a minute lumen containing red cells could sometimes be seen.

These lesions resemble in part, those described in "allergic granulomatosis" (25). This latter disease is characterized by the presence of allergic asthma, absent in our cases, and the presence of numerous eosinophils in the lesions, present in only small numbers in the hepatic granulomas in one of our cases. These lesions also resemble those described in one case reported as sarcoidosis (26) and in one patient with generalized Hodgkin's disease (27). There is also some resemblance to the lesions in giant cell or temporal arteritis (28). This latter disease is not generally fatal and occurs among older people, while one of our patients was 18 years old. Despite the similarities to these other conditions, it is our opinion that the two cases observed in our laboratory and possibly others of like character (29) warrant consideration as a separate entity.

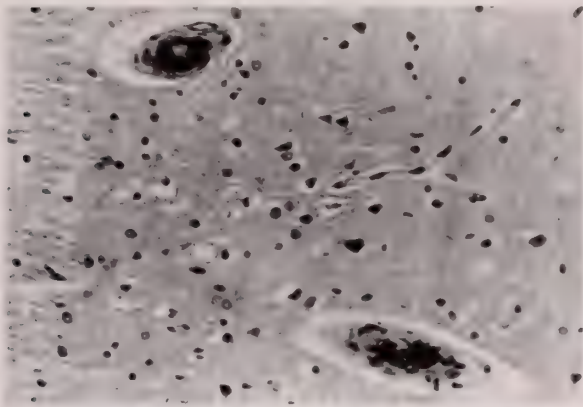


FIG. 5. Small parenchymal arteries with hematoxylin bodies and a slight endothelial hyperplasia in lupus erythematosus. Hematoxylin and eosin, $\times 150$.

LUPUS ERYTHEMATOSUS

The cerebral vessels are involved in only a small proportion of cases of disseminated lupus erythematosus. When present, the involvement affected the small meningeal and parenchymal arteries, and this was associated with scattered small zones of infarction, mainly in the cerebral cortex (30). As in other organs (31) the affected vessels showed a rather marked hypertrophy and hyperplasia of mesenchymal cells, probably of endothelial origin, which passed from the wall into the lumen narrowing, or completely occluding the lumen. Some of these cells resembled fibroblasts and were associated with the deposition of collagen fibers. Portions of the original wall and the newly formed connective tissue occasionally showed fibrinoid change. In addition there were deposits of a granular, eosinophilic or basophilic material (Fig. 5) within the proliferating cellular mass and sometimes clearly within a space representing the lumen. The basophilic materials, often present in considerable quantities, were stained by the Feulgen method and represent hematoxylin bodies (32, 33).

MOSCHCOWITZ DISEASE: (THROMBOTIC THROMBOCYTOPENIC PURPURA)

The cerebral lesions in cases presenting the classical clinico-pathological features (34-36) of this disease, including the severe neurological abnormalities which are characteristic of it, consisted of the deposition of a granular eosinophilic material in the lumens of capillaries and possibly the smallest arterioles and venules (Fig. 6). This was associated with a moderate hypertrophy and hyperplasia of the endothelial cells, generally into the lumen. In our cases, no other pathological process was recognized to which the observed changes could be secondary, although other observers have described such antecedent disease processes and have suggested that this condition is not an entity (37).

NEOPLASTIC DISEASES

In neoplasms of the cerebrum, marked hyperplastic and proliferative changes are noted in the cerebral capillaries, particularly with glioblastoma multiforme.

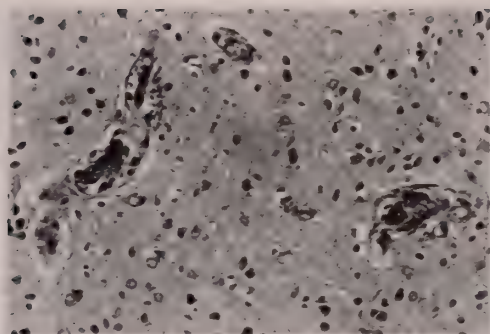


FIG. 6. Intracerebral vessels with granular thrombi in Moschcowitz disease. Hematoxylin and eosin, $\times 350$.

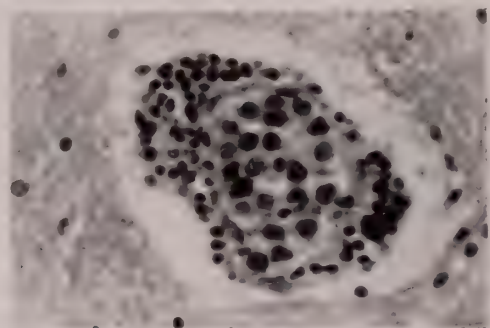


FIG. 7. Vessel containing lymphosarcoma cells and revealing a perivascular lymphocytic inflammatory infiltrate. Hematoxylin and eosin, $\times 330$.

Some of the larger vessels may be thickened, fibrotic and thrombosed, and this may be related to the zones of necrosis common in this tumor. In addition, tumors may increase the supratentorial pressure causing a herniation of the anterior portion of the hippocampal gyrus beneath the tentorium compressing the veins draining the brain stem and causing hemorrhages into that tissue. More rarely, the posterior cerebral arteries are compressed by the same mechanism causing infarction in the occipital lobe.

We would like to record the case of a patient with lymphosarcomatosis in which there was a profound chronic brain syndrome indicative of diffuse cerebral damage. At autopsy, it was apparent that a lymphosarcomatous mass had ruptured into the inferior vena cava seeding malignant cells throughout the body. There were moderate numbers of vessels in the brain containing large numbers of malignant cells, which showed infiltration of their perivascular spaces by large numbers of lymphocytes (Fig. 7). This inflammatory lesion was the only morphologic change to which the profound neurological symptoms could be attributed.

SUMMARY AND CONCLUSIONS

Attention is drawn to some of the less common disease processes affecting the blood vessels of the brain. Although arteriosclerosis and hypertension affect the

brain far more frequently, these uncommon processes warrant consideration in cases in which vascular disease of the brain is indicated, but arteriosclerosis and hypertension appear to be excluded.

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THE SPINAL CORD IN INIENCEPHALY*

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AND

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Iniiencephaly is a congenital anomaly characterized by (1) deficiency of the occiput in the region of the foramen magnum, (2) spina bifida, and (3) marked hyperextension of the head and neck of the fetus. The name was first used in 1836 by Saint Hilaire.¹ Lewis² in 1897 recorded 22 cases and subdivided the condition into categories he termed iniiencephalus clausus, iniiencephalus apertus with small encephalocoele, and iniiencephalus apertus with encephalocoele larger than the cranial content. In 1904 Ballantyne³ added 7 more cases and emphasized the differences between "iniiencephaly" and "aniencephaly with retroflexion." In 1927 Welz and Lieberman⁴ published a case and for the first time reviewed the literature concerning the possible etiologic factors. In 1939 Brodsky⁵ listed 57 cases accumulated since Saint Hilaire's showing an 8 to 1 predominance in the female, and an equal incidence in premature and full term infants. Since 1939, 20 more cases have been published,⁶⁻¹³ bringing the number of reported cases to 77.

In none of the cases was there a complete description of the central nervous system. Dastur¹² gave a good account of the gross features but did not include any microscopic findings. The spinal cord in iniiencephaly was also not mentioned in the detailed discussions of spinal cord malformations by Gagel¹⁴ and Ostertag.¹⁵

It is the purpose of this paper to describe the spinal cord malformations in this case of typical iniiencephalus.

CASE REPORT

The patient was a 4 pound, 15 ounce white female, stillborn at the 36th week of gestation to an Rh negative, gravida I, para 0, 19 year old mother. The presentation was left sacro-anterior. Delivery by double footling breech extraction with the help of Piper forceps was accomplished with great difficulty by Dr. Leo Seltzer.

The mother was healthy although she had signs of albinism. The iris, however, was colored. The past history of the mother was not relevant. The obstetrical history was considered unreliable inasmuch as the mother insisted that her menstrual periods had occurred each month during the entire period of pregnancy.

Pertinent Gross Autopsy Findings

White female stillborn measuring 43 cm. in length, weighing 2,260 gm. Head fixed in dorsal hyperextension with typical features of short bulging neck of iniiencephaly and bilateral club foot (equinovarus) (Fig. 1). There was a pre-

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FIG. 1. Iniencephalus with bilateral club foot.

auricular appendage on the left cheek. Internal anomalies consisted of large left diaphragmatic defect with prolapse of spleen, stomach, parts of left liver lobe and of colon into left pleural cavity with subsequent compression of left lung and mediastinal shift to the right. The shallow abdominal cavity showed abnormal secondary peritoneal attachment of appendix, cecum and right colon to the undersurface of liver and gallbladder. The spine revealed marked lordosis and shortening of the cervico-dorsal portion with posterior occult rhachischisis and segmental disarrangement of this portion. The rhachischisis was covered by the fixed hyperextended head and was continuous with the usually large foramen magnum (3.5 cm. in diameter). In this area much fresh hemorrhage in the soft tissues and in extradural space of the spinal canal was encountered. The cerebrum showed only blunting of the occipital poles. The cerebellum, pons and medulla were cranio-caudally elongated and laterally compressed, protruding partly through the large foramen ovale into the spinal canal (Fig. 2). The spinal cord is unusually short (63 mm.) presenting in its upper half, corresponding to the area of rhachischisis, as a persistent medullary plate continuous with the floor of the 4th ventricle and connected with it through a wide median foramen (Fig. 3). The ventral aspect of the cord shows almost complete separation in the cervical portion with absence of the pyramidal crossing and marked redundant kinking of the left half of the cord (Fig. 2). In the lumbar portion a complete midline separation of the cord was present in a short area (Fig. 3e).

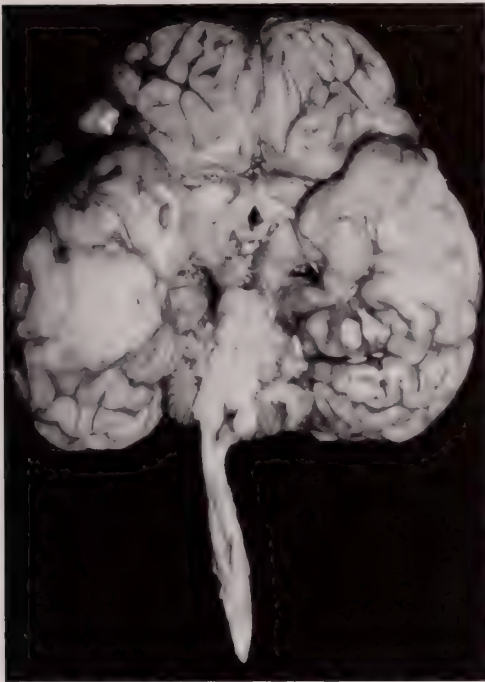


FIG. 2. Ventral view of the brain and spinal cord.

GROSS AUTOPSY DIAGNOSIS (ABRIDGED)

Iniencephalus with herniation of cerebellum and medulla through enlarged foramen magnum; cervicodorsal severe lordosis with dorsal rhachischisis and myeloschisis; lumbar diastematomyelia; left sided diaphragmatic defect with prolapse of many abdominal viscera into left pleural cavity; bilateral club foot.

Microscopic Description of Spinal Cord

The cord was completely sectioned in numerous blocks and studied in hematoxylin-eosin and luxol fast blue preparations for myelin. In the most important areas serial sections were made.

Cervical Portion of Spinal Cord: The exposed dorsal surface was lined by tall ciliated columnar ependymal cells which in some parts seemed to be pseudostratified (Fig. 3b and c). At the lower portion this dorsal surface was dimpled and from it islands of spongioblasts and mature glial cells extended into the white matter. The dorsal funiculi were found at the lateral margins. Only on the left side was there a vague demarcation between the fasciculus cuneatus and gracilis. The anterior margin of each side of the cord was occupied by the dorsal root at the outer third, a small lateral fasciculus at the middle third, and anterior rootlets at the medial third. All the nerve fibers of the dorsal funiculi, the dorsal root, and the lateral funiculi stained well with luxol fast blue indicating myelination. The entire medial border of each side of the cord was filled with unmyelinated

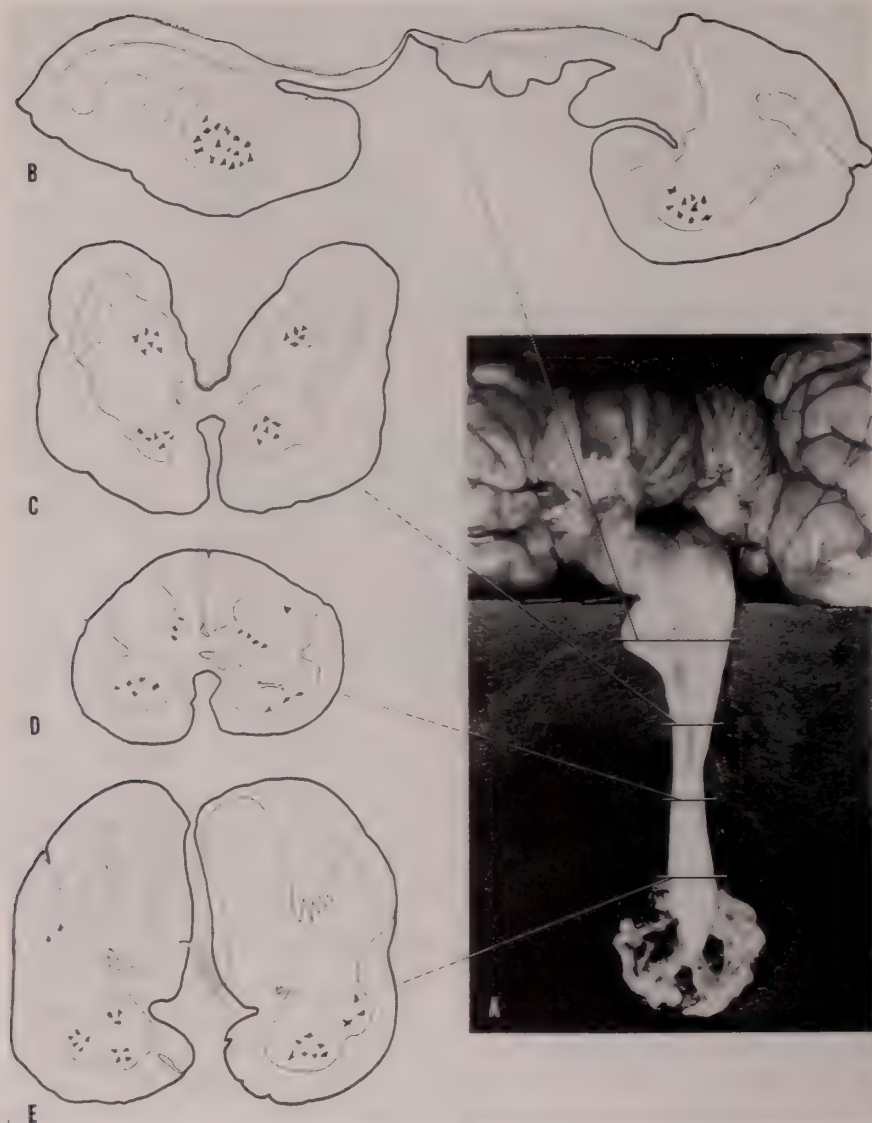


FIG. 3. Dorsal view of the spinal cord (a). Arrows point to schematic drawings at different (b, c, d, e) cord levels.

fibers of the uncrossed pyramidal tract. The anterior white commissure was quite thick and was seen to possess myelinated fibers, some of which ended in the reticular substance. There were large neurons in the usual position of the anterior gray commissure which could not be definitely outlined. At the level of maximal kinking, the white commissure was stretched and some fibers of the left ventral pyramidal tract were carried with it (Fig. 3b). In the upper cervical cord, the gray matter was an indiscriminate mass of neurons and nerve fibers. In the rest

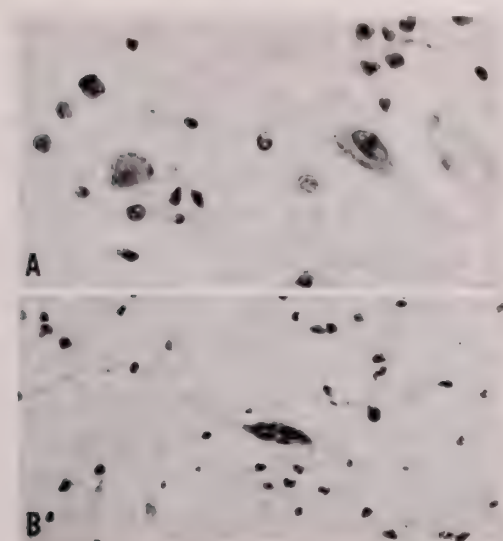


FIG. 4. Ectopic neurons in posterior (a) and anterior (b) white columns.



FIG. 5. Lumbar cord with accessory central canals (a), dysraphic syringomyelia (b), and accessory posterior horns (c).

of the cervical cord the gray matter was more definitely shaped into posterior and anterior columns. The posterior column was divided into cervix, caput, and apex and there was an accessory caput more dorsal to the main caput. The Clarks column could be easily identified at the base of the cervix (Fig. 3c). The anterior column showed orderly collections of large anterior lateral and medial multipolar motor ganglion cells.

Thoracic Portion of Spinal Cord: The dorsal defect in the upper thoracic cord gradually tapered off into a definite central canal. In the rest of the thoracic cord, this canal coursed more anteriorly. The dorsal funiculus, the dorsal root, the lateral funiculus, and the ventral root also gradually assumed their normal position (Fig. 3d). The left ventral pyramidal tract remained large while the right ventral pyramidal tract became small. Some tall columnar cells were lining

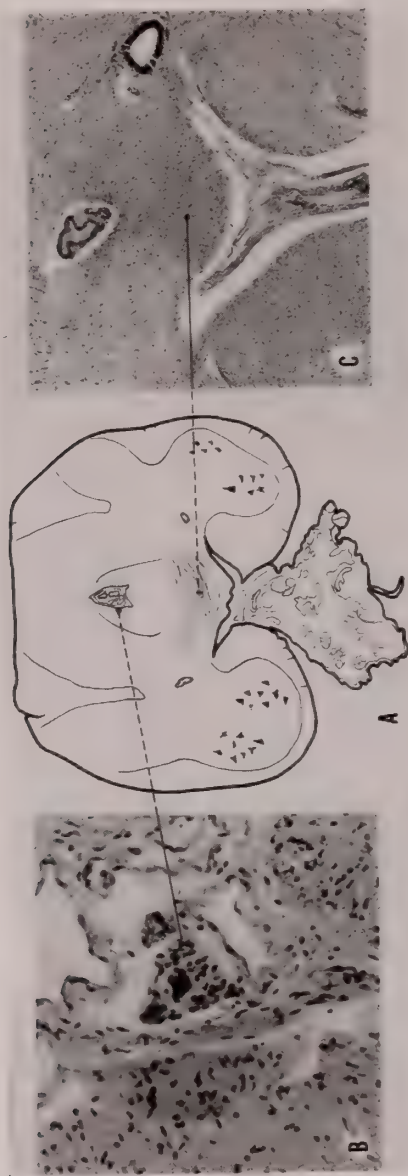


FIG. 6. Lumbar cord (a) with spinal ganglion inclusion (b) and pyramidal crossing (c).

the anterior median fissure. A few displaced neurons appeared in the fasciculus gracilis and in the anterior white matter (Fig. 4a and b). Groups of spongioblasts were occasionally seen around the central canal. The gray matter was essentially normal. The intermediate gray mass was well developed. In this area the united dorsal white columns formed a dorsal bulge, while the posterior gray columns ventral to it were partly fused in the midline.

Lumbo-Sacral Portion of the Spinal Cord: The dorsal median fissure was shifted to the right and gradually became indistinct as it proceeded downwards. About the middle of the upper third of the lumbar bulge, accessory posterior horns appeared separated by an eccentrically located row of numerous small canals lined by ependymal cells, and by an area of dysraphic gliosis with central cavity (Fig. 5). The main central canal also began to divide at this level. This change actually presaged the duplication of the cord at about the middle and lower third of the lumbar bulge. A duplication of the cord was thus formed, each side having a true lateral dorsal and ventral gray column and a medial asymmetrical accessory or rudimentary dorsal and ventral gray column (Fig. 3e). Nerve fibers were seen to arise from the accessory ventral gray columns and together with the leptomeninges filled the space between the two cords.

At the lower lumbar bulge and at the sacral area, the two cords fused again. A part of the meningeal tissue in the dorsal fissure was pinched off forming an inclusion in the middle of the dorsal funiculus. In this space small pieces of pia-arachnoid membrane with ganglion cells of spinal type were seen (Fig. 6a & b). Crossing of the pyramidal tracts finally occurred at this level of the cord (Fig. 6a & c). The central canal remained divided.

The medulla oblongata, the pons, the cerebellum, and the cerebrum were histologically essentially normal.

COMMENT

In this iniencephalus the seven main anomalies of the spinal cord were, Hypoplasia of the entire cord, dorsal myeloschisis, dysraphic syringomyelia: heterotopy of neurons in the white columns, diastematomyelia, inclusion of neural crest tissue in the posterior white column and lumbar pyramidal decussation. All these anomalies have been observed separately before but have to our knowledge not been reported in the cord of one individual. They indicate a deep seated early disturbance of the development, closure and subsequent differentiation of the medullary plate. The disturbance is apparently coordinated with the present anomalous development of the spine and occiput.

SUMMARY

1. The spinal cord findings in iniencephaly are described for the first time.
2. Seven different spinal cord anomalies were demonstrated in this case.
3. The malformations of the nervous system were associated with corresponding anomalies of the axial skeleton and occiput.

ACKNOWLEDGMENT

The authors wish to express their thanks to the Armed Forces Institute of Pathology for the preparation of the photomicrographs and of the drawings.

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PATHOGENESIS OF ARTERIAL SCLEROSIS, IN THE LIGHT OF MODERN VIEWS ON VASCULAR MICROANATOMY AND THE ROLE OF POLYSACCHARIDES IN WOUND HEALING

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INTRODUCTION

The primary object of the present study is to attempt to bring to bear, on the study of vascular lesions, the information now available concerning the more general aspects of the repair process as seen from the examination of healing in other tissues and especially of cutaneous wounds (1-3). We entirely concur with the view expressed by Prior and Hutter (4) that:—

“Despite the fact that arteriosclerosis is the leading cause of morbidity and mortality today, one cannot avoid the conclusion that our knowledge of its pathogenesis is shamefully deficient. . . . With the main interest focussed upon the method of lipid transport through the vascular endothelium, it is understandable why the basic processes of injury and repair within the arterial subendothelial zone have been ignored”.

Our interest lies, ultimately, in attempting to understand, through a study of the repair process in general, the pathogenesis of those diseases which are most frequently associated with ageing or which are generally referred to as “degenerative diseases”.

Our experimental findings indicate that, as in the skin, so too in arteries the supervention of scar tissue may, and in some instances undoubtedly does, depend in large measure on the intensity and/or duration of a *single* acute injury. It is widely accepted that superficial abrasions of the skin heal by regeneration (i.e. with maintenance of the original architecture and without scar formation), while deep and, if long-maintained, even *superficial* cutaneous injuries heal by repair, i.e. with architectural distortion and scar formation. It is generally believed, or at least implied, that sclerosis of arteries is usually a gradual process commencing relatively late in life. It seems to us that at least *some* forms of arterial sclerosis may represent the end result of a *single*, acute injury inflicted months or perhaps even years prior to recognition of the terminal picture. Such a form of vascular sclerosis is certainly theoretically possible, corresponding, as it does, either to scar formation in the skin or to that type of hepatic cirrhosis which is a sequel to a single attack of acute hepatitis.

Cutaneous scars are always easily visible, being located on the body's surface. The presence of hepatic scars or sclerosis may be displayed by liver biopsy or are frequently suspected by the attendant disturbances of hepatic functions. Localised vascular scars are rarely recognised during life, while *diffuse* scarring of

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blood vessels, following a single episode of injury, to our knowledge has not even been considered as a pathological or clinical entity. Yet this orientation towards the pathogenesis of some types of vascular and especially coronary sclerosis may have much to contribute to our attack on this important medical problem.

Elsewhere we have drawn attention to changes in dermal, vascular and other connective tissue fibers apparently resulting from, or at least associated with cutaneous injuries of several types (1, 2, 5). Evidence is also available that alterations in connective tissue fibres, such as those named by us "pseudo-elastic fibres" or "pseudo-elastosis", seem to predispose to mineralisation (2). There is, moreover, ample evidence to show that mineralisation of connective tissues, in many sites, is in some way bound up with the state of their mucopolysaccharides (6-8). There is indication, too, that metastatic calcification occurs only in sites of previous injury and that the peculiarity of such injured loci, which may be responsible for their susceptibility to mineralisation, is their polysaccharide content which invariably increases during the repair of the injured connective tissues (9-11). The essential point about this argument and these findings is that the deposition of minerals (and possibly also of lipids) in vascular tissue may not be primarily a function of the level of the minerals and lipids in the circulating blood, but rather of the preceding alterations in the ground substance of arteries and other connective tissues which predispose them to mineralisation or lipoidosis.

We have also provided evidence that the so-called elastic membranes in arteries (of all sizes) are not homogeneous, but are probably constituted of collagen-like "cores" around which spiral elastic-like fibrils. The amplitude of these spirals varies with the size of the artery. This complex (collagen-like core plus enveloping elastic helix) is enclosed by reticulin fibres which, in turn, are coated by a sleeve of polysaccharides (12).

The integrity of the apparently important collagen-like cores seems to depend on the ability of their enveloping constituents to regenerate new fibrillar components within or around the "cores". On this basis and from modern knowledge of fibre-genesis in healing wounds, the susceptibility to injury of the vascular elastic membranes (V.E.M.'s) would be, at least in part, a function of the turnover of the polysaccharide sleeves around the cores of the membranes. Any interference with polysaccharide metabolism may be expected to result in some disturbance of the integrity of the related V.E.M.'s themselves. Furthermore, our earlier studies indicated that only when the collagen-like cores of the V.E.M.'s are disrupted is their normal regeneration superseded by *repair*, i.e. by architectural distortion consequent on fibrosis or scar formation in the injured site.

In these latter circumstances, i.e. where injury is sufficiently severe to result in scar formation, the accumulation of polysaccharides in sites of vascular injury and the subsequent intramural fibrosis is, in our view, directly comparable with the seemingly identical sequence of events during the healing of cutaneous injuries (13-15), where mucopolysaccharide accumulation seems to be an essential precursor to collagen deposition.

If damage to these collagen-like cores ultimately proves to be as fundamental

as we believe in determining the reactions of arteries to injury, then vascular injuries in lupus etc. become more easily understandable, and a much wider range of arterial lesions than hitherto suspected may yet come to be included within the framework of Klemperer's basic concept of the "collagen diseases".

In order to produce, consistently and expeditiously, widespread injury to the vascular system, toxic doses of calciferol were administered to rats according to the method recommended by Ham and Lewis (16) and more recently by Gillman and Gilbert (17). As will be seen from the following brief report, our views outlined above receive considerable substantiation from the study of the serial events in vessels, of these rats, which were injured and which subsequently became mineralised, followed by regeneration or sclerosis.

EXPERIMENTAL

Only the essential features of the experimental procedure need be mentioned here. The experimental material comprised heart and coronary vessels, four separate parts of the aorta of each rat, spleen, stomach, intestine and other tissues from 155 male and 40 female rats, weighing 160 to 210 grams, which had received between 24,000 and 72,000 units of calciferol daily, by mouth, for five consecutive days only. Thereafter, post-mortem studies were conducted on moribund animals or on rats sacrificed between four and three hundred days after the initiation of the experiments.

Serial wax sections of these tissues, fixed in formalin, were stained by the methods previously outlined (1, 2, 3, 12, 18), to demonstrate particularly cytology and elastic, collagen and reticulin fibres, and by the periodic acid Schiff (P.A.S.) and von Kossa (V.K.) routines (to demonstrate polysaccharides and mineralisation respectively). The alcoholic toluidine blue method, recommended by Glick (19) was also used routinely to identify metachromatic mucopolysaccharides in connective tissue ground substance and in mast cells.

For comparison with the experimental material aorta, carotids, pulmonary and other medium and small sized arteries and arterioles were obtained, at post-mortem, from human subjects 10 to 30 minutes after acute traumatic deaths or dying from various diseases.

OBSERVATIONS

Here, too, only observations relevant to our argument will be briefly recorded.

The initial *aortic lesions*, appearing 6-15 days after the first dose of calciferol, were localised *around* those medial vascular elastic membranes (V.E.M.'s) located just deep to the intima; the latter usually remained intact until several weeks after the initiation of the experiments. This early calcification of the injured aortic V.E.M.'s is invariably associated, initially, with the local accumulation of non-sulphated P.A.S.-positive polysaccharide and the disruption of the reticulin sleeves (Figs. 1 and 2). If the dose of calciferol has not been unduly great, this initial mineralisation may resolve even within the next 6-10 days, whereafter the tissue *between* the injured membranes then becomes laden with metachromatic mucopolysaccharide. Such injury may ultimately be resolved by

regeneration of the peri-elastic membrane coating (of reticulin and other constituents) *without* any fibrosis.

However, if the aortic calcification induced is severe or prolonged (as occurs with the larger doses of calciferol mentioned above), then the *cores* of the mem-

FIG. 1



FIG. 2

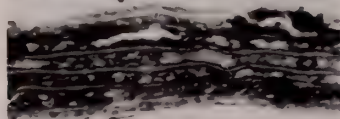


FIG. 1. High power view of the *thoracic* aorta from a rat one day after the last of five daily doses of 24,000 units of calciferol, to demonstrate the heavy mineralisation *around* and *between* the elastic membranes. The central "cores" of the latter can be seen as paler non-mineralised streaks within the heavy von Kossa positive material. Von Kossa method. $\times 250$.

FIG. 2. Serial section to Fig. 1 to show intact elastic membranes surrounded by darkly staining metachromatic polysaccharide which is also aggregated in pools around the uppermost elastic membrane in this figure. Alcoholic toluidine blue only. $\times 250$.

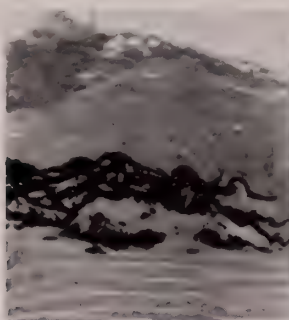


FIG. 3

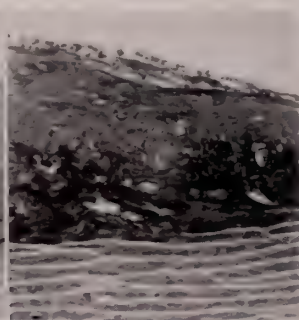


FIG. 4

FIG. 3. A patch of residual calcification in the ascending aorta of a rat 40 days after the last of five daily doses of 24,000 units of calciferol. Note the fragmentation of the elastic membranes in the inner portion of media, surrounded by excessive minerals. The elastic membranes of the outer portion of the media are clearly shown to be intact. There has been fibrosis around this area of residual calcification with a plaque projecting towards the intima. Von Kossa preparation. $\times 150$.

FIG. 4. Serial section of same aorta as Fig. 3, to show massive deposition of metachromatic mucopolysaccharide (pools of dark-staining material at inner portion of media corresponding to areas shown as calcified in Fig. 3). The elastic membranes, in this damaged and fibrosing area, are clearly fragmented as compared with those in the outer portion of the media which are apparently still intact and undamaged. Alcoholic toluidine blue only. $\times 150$.

branes themselves may become disrupted and fragmented. Lesions of this latter order are *repaired* by fibrosis and, in the aorta, later even by cartilage or bone formation. As in the genesis of all scars in damaged connective tissue, fibre formation is regularly *preceded* by, and apparently dependent upon, the prior accumulation of mucopolysaccharides (Figs. 3 and 4). In these latter circum-

stances, the intima may become involved in the pathological process, but only *secondarily*. The sequence of events here is apparently just the reverse of that outlined by Hueper (20) and his supporters, who maintain that medial lesions are usually secondary to intimal damage.

In the *coronary vessels*, calcium deposition occurs between the third and sixth days, i.e. earlier than in the aorta. This calcium in the coronaries, almost invari-

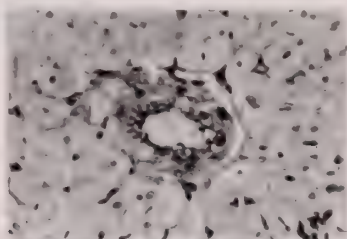


FIG. 5

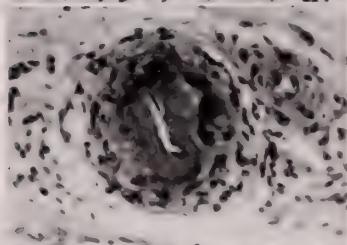


FIG. 6

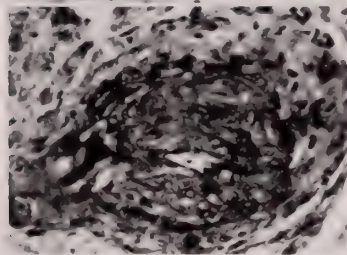


FIG. 7

FIG. 5. Normal medium-sized coronary artery of a rat showing wavy, indented P.A.S. positive internal elastic membrane. P.A.S. stain. $\times 220$.

FIG. 6. Medium-sized coronary vessel in a rat 5 days after the last of five consecutive daily doses of 24,000 units of calciferol, to demonstrate broad, P.A.S. intensely positive, internal elastic membrane and deposition of "pools" of P.A.S. positive material above and around the vessel. There is also an increased peri-vascular cellularity indicative of incipient inflammation. P.A.S. method. $\times 220$.

FIG. 7. Markedly thickened cellular, pre-fibrotic medium-sized coronary vessel in the heart of a rat 40 days after the last of five daily doses of calciferol. Note also narrowing of lumen and pools of metachromatic mucopolysaccharide (especially well shown at 6 o'clock and between 12 and 2 o'clock on the walls of this vessel). Alcoholic toluidine blue only. $\times 220$.

ably disappears completely during the next 6-8 days. However, several weeks later residual injury to the coronaries is consistently evinced by the marked thickening of the internal elastic membranes which become wide and heavily stainable by the P.A.S. routine (cf. Figs. 5 and 6). This reaction, in turn, is succeeded during the ensuing weeks by all the histological changes characteristic of healing injuries, namely by round cell, fibroblast and metachromatic polysaccharide accumulation associated with narrowing of the vascular lumen (Fig. 7).

"True" scar formation is evident in the coronary arteries only 90 to 120 days after the initial injury when, as in ageing cutaneous scars, cellularity diminishes and collagen increases markedly (Figs. 8 and 9). Luminal distortion also supervenes at this time in consequence of what is probably the equivalent in the coronaries of contracture in cutaneous scars (Figs. 8 and 9). Similar lesions have been encountered in damaged mesenteric vessels in our rats. In the latter location, calcification of the blood vessels has been found to be followed by replacement of almost the entire wall of the mesenteric arteries by a tissue indistinguishable from the new connective tissue in healing excised cutaneous wounds (3). This early stage in scar formation in the arteries occurs at about 120 days after the

FIG. 8

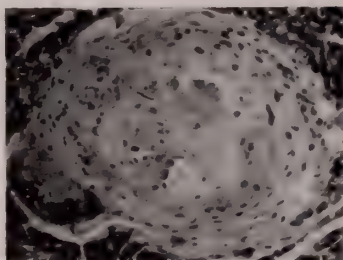


FIG. 9

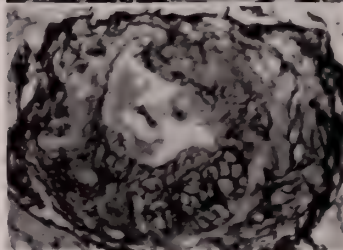


FIG. 8. Coronary from rat 188 days after the first dose of calciferol, and 71 days after a second course of 5 daily doses of 36,000 units. Note gross distortion with virtual occlusion of lumen, loss of mural architecture, diminution in mural and peri-vascular cellularity and collagenisation of wall. Ponceau 2R/light green. $\times 250$.

FIG. 9. Coronary from another rat which received the same treatment as that in Fig. 7 and was killed at the same time—showing marked increase in and abnormal pattern of reticulin, with luminal distortion. Wilder's method. $\times 330$.

initial injury, and is succeeded by fibrosis of arteries so affected (see Figs. 10 and 11).

Among the important findings emerging from this study is the difference in the time taken for fibrosis (collagenisation) and other changes to supervene in vascular as opposed to cutaneous injuries (Table I). In the latter, new fibroblasts are numerous by the fourth day, and fibrosis commences by the sixth day after wounding; if healing is uncomplicated, fibroblasts decrease, and collagenisation in cutaneous wounds is well marked by 15–20 days. Coronary arteries subjected to a *single* insult become highly cellular (due to fibroblasts etc.) only at 30–40 days after the trauma; sulphated and other polysaccharides persist in such injured sites in arteries for 60–100 days and true fibrosis of acutely injured vessels becomes well marked only 90–120 days after a single injury, at least by calciferol.



FIG. 10

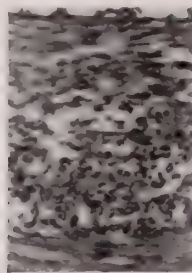


FIG. 11

FIG. 10. Mesenteric artery from same rat as Fig. 7 to show replacement of almost two thirds of its thickness and entire circumference by new highly cellular connective tissue (B) which was rich in metachromatic mucopolysaccharides. Some muscle remains around periphery. Alcoholic toluidine blue. $\times 32$.

FIG. 11. High power view of wall at A in Fig. 10 to show numerous fibroblasts, possibly some regenerating smooth muscle and intercellular spaces rich in metachromatic mucopolysaccharides. At this power the new connective tissue, forming the greater part of the vascular wall, is not distinguishable from that observable in healing cutaneous wounds. Alcoholic toluidine blue. $\times 360$.

TABLE I

Comparison of histopathological and histochemical changes in healing cutaneous wounds and in injured coronaries in rats

Indicator	Time in Days	
	Cutaneous wounds	Coronary injuries
Leukocyte + round cell increase.....	2-4	4-20+
Fibroblast increase.....	2-6	20-60
Fibroblast decrease.....	12-20	80-120
P.A.S. + ve material increase.....	3-6	4-80+
P.A.S. + ve material decrease.....	6-12	60-120+
SO ₄ M.P.S. increase.....	3-6	6-80+
SO ₄ M.P.S. decrease.....	6-12	100+
Collagen increase.....	4-20	40-140+
Contracture.....	8-30+	80+

The possible significance of these findings in understanding the pathogenesis of coronary disease will be discussed briefly below.

COMMENTS

Perhaps the most important fact emerging from this study is that the sequence of events in the healing of vascular and cutaneous injuries is broadly the same (see Table I). As for the vascular lesions—injuries to cells or preexisting fibres comprising the blood vessel wall, at least of the type described above, are usually followed by the simultaneous accumulation in the injured sites of minerals and non-sulphated polysaccharides. The latter alterations may be followed by *regeneration* of the original vascular architecture (comparable with that occurring after superficial cutaneous injuries) or by *repair*, depending on the intensity and or the duration of the vascular lesions. Such repair invariably implies loss

of the original architecture, consequent on fibrosis or scar formation. This scar formation, in turn, is heralded by the localised accumulation of *metachromatic* (sulphated) mucopolysaccharides, associated with fibroblast aggregation and later by new collagen fibre formation in the sites of injury (21).

As shown above, an almost identical series of morphologically and histochemically demonstrable events is encountered in healing cutaneous wounds, in resolving metastatic calcification and even in the healing of noncalcifying vascular lesions, induced by calciferol, not only in vessels, but also in the gastric and colonic walls, kidneys and elsewhere in our rats. The only exception to this rule—i.e. occurrence of scar formation as a sequel of severe or prolonged injury by calciferol—occurs in the case of the spleen. As indicated elsewhere, the spleen frequently undergoes extensive necrosis (haemorrhagic or ischaemic) at 8–12 days after the first doses of calciferol. However, by 18–20 days after the initiation of the experiments these extensive splenic lesions heal by complete regeneration of this organ. Such healing of extensive connective tissue injuries, without detectable scarring, seems to be peculiar to highly cellular reticulo-endothelial organs.

Of some theoretical, and perhaps even practical importance is, firstly, the fact that a *single* trauma to the coronary arteries in rats may be followed, months later, by sclerosis, and secondly, that in the case of some arteries (coronaries, mesenterics etc.) such sclerosis supervenes in rats only 3–5 months after the acute injury has been inflicted. This long time, which is apparently required for true vascular sclerosis to occur after the acute injury, corresponds to about $\frac{1}{12}$ of the rat's lifespan of 36–48 months. If these time relations hold also for man, then coronary sclerosis at the age of 40–50 years may perhaps be the outcome of *acute* vascular injuries inflicted *years* before. The aorta may be particularly susceptible to injury between the ages of 12 and 20, when this artery is probably growing rapidly, both in length and diameter, to conform with the marked increase in trunk length occurring during this age period. These possibilities seem to merit further investigation in man.

To carry the comparison between cutaneous and vascular injuries further—we have already shown that superficial cutaneous injuries heal by regeneration while scar formation in the skin is an invariable sequel of lesions extending into the stratum papillaris of the dermis (12). Our findings in arteries indicate that with small doses of calciferol, calcification, which always occurs *around* and *not* within the vascular elastic membranes (12) may resolve in a few days and be followed by regeneration of the injured tissues but without scar formation. However, much more severe and more prolonged peri-membranous calcifications, attendant on the administration of larger doses of calciferol, usually lead to disruption of the cores of the vascular elastic membranes. Lesions of the latter order are invariably followed either by repair or scar formation, or, especially in the aortic media, by persistent calcification, or cartilage and even bone formation. As in the skin, ruptured or severely damaged elastic fibres or membranes did *not* regenerate even 300 days after injury.

According to our views, then, at least some types of vascular sclerosis are consequent on primary injury to the elastic membranes of the *media*, apparently following disturbances in the polysaccharide metabolism normally involved in maintaining the integrity of the collagen-like cores of these vascular elastic membranes. The localisation of lesions to particular segments of the arterial tree, such as those here recorded, may perhaps be related to the more rapid rate of turnover of polysaccharides in those portions of the vascular tree where normal wear and tear, and therefore the normal rate of *regeneration*, is greatest. The increasing incidence of vascular sclerosis as well as the increasing concentration of mucopolysaccharides in the aortic walls associated with ageing (22) may perhaps be attributable to the decreasing capacity of the ageing organism to maintain normal regenerative processes. The organism would then fall back on the second line of defence—namely repair, with its attendant fibrosis and architectural distortion.

Evidence has also been adduced elsewhere to show that the physico-chemical state of plasma lipid may be profoundly influenced by sulphated mucopolysaccharides, like heparin, acting in concert with circulating calcium ions (23). Our *in vitro* experiments demonstrated that the addition of heparin to freshly collected blood, or of heparin *plus* a free source of calcium ions to *serum* led to an almost immediate breaking of the chylomicron emulsion with the consequent formation of a lipid-rich cream on the surface of the plasma or serum and resultant clearing of opalescence. On the basis of this finding it seems reasonable to suggest that, on contact with connective tissues rich both in mucopolysaccharides and minerals (such as in sites of injury in vascular walls mentioned above), the emulsion of lipids in the circulating plasma may rapidly be broken with consequent immediate deposition of the plasma lipids in sites of repair (as in the arterial media etc.). Lipid deposition would then be only secondary to pre-existing alterations in the fibres and ground substance comprising the walls of arteries.

It would seem that the combination of Hueper's views (20) and those presented here may be more useful in accounting for the pathogenesis of the several different forms of vascular degeneration which have become so important in modern medicine. Apart from allowing for the resolution of the seeming discrepancy in the findings of various workers, concerning the priority of medial as opposed to intimal lesions, another satisfying aspect of our findings, and the interpretations thereof here presented, is the seeming uniformity in the repair of damaged connective tissue lesions throughout the body—a uniformity which may be anticipated simply from the basically similar tissues involved in vessels, dermis and elsewhere.

In the light of the above facts and hypotheses, injuries and degenerations in blood vessels and in other organs and tissues may yet prove to be due to disturbances in the metabolism of that important end-organ—the mucopolysaccharides and other carbohydrates in the connective tissue ground substance throughout the organism—which is directly or indirectly involved in maintaining the integrity, regeneration and repair of collagen, elastic and other fibres.

SUMMARY

1. The hypothesis is put forward that at least some forms of vascular injury originate as medial damage and might profitably be considered in terms of the histogenesis and histochemistry of the healing of any injured connective tissues—irrespective of location.

2. This proposition is based on the following findings:—

a. Vascular elastic membranes (V.E.M.'s) are not homogeneous but seem to be constituted of central collagen-like "cores" surrounded by elastic-like, fine fibred helices and reticulin and polysaccharide sleeves.

b. Injuries to these "elastic" membranes, such as those inducible with toxic doses of calciferol in rats, are initially manifested by calcium deposition in the polysaccharide sleeves *around* the still intact "cores" of the V.E.M.'s of the inner part of the media. Such peri-membranous calcifications are invariably associated with localised increases of non-sulphated polysaccharides and may resolve with regeneration of tissue, i.e. without scarring.

c. If severe or prolonged, alterations in the peri-membranous components of the medial V.E.M.'s may be followed by fragmentation of their collagen-like "cores", the maintenance of the integrity of which seems to be a function of their polysaccharide and reticulin "sleeves". Lesions of such severity seem invariably to be followed by *repair*, i.e. sclerosis with the consequent inevitable architectural distortion and secondary intimal scarring.

d. Such sclerosis in arteries, as for scars in healing dermal injuries, is regularly associated with sulphated mucopolysaccharide accumulation which, as in cutaneous injuries, precedes fibrillogenesis. Severely damaged V.E.M.'s were not replaced during the course of these experiments.

It has been shown that a single acute but severe injury to arteries in rats may be followed, months later, by true scar formation, i.e. sclerosis.

3. The serial histologically and histochemically definable events in healing cutaneous wounds and arterial lesions have been compared. The *sequence* of events in repair is the same in both, but the reactions culminating in scars occur much more slowly in arteries. Increase in P.A.S.-positive polysaccharides is maintained much longer in arteries, while sulphated polysaccharide increase and true fibrosis in arteries occurs later, often only many weeks after the infliction of the injury.

4. The susceptibility of particular parts of the arterial tree to age changes and to various lesions, may perhaps be a function, not only of the nature of the injury, but especially of the rate of turnover of muco- and other polysaccharides during regeneration of the normal "wear and tear" injuries to the collagen-like "cores" of the V.E.M.'s.

5. Evidence is here presented, from experiments in animals, that muco- and other polysaccharides, which play a critical role in the repair of most connective tissue lesions, seem also to be important in the repair of *vascular* damage. Perhaps the accumulation of polysaccharides in sites of healing arterial injuries may play a more important role in lipid and mineral deposition in vessels than the quantity and quality of the fats and minerals in the circulating plasma.

6. In the light of the above findings some forms of arterial disease may yet prove to result from primary disturbances in the intramural polysaccharide metabolism which seems to play an important role both in the regeneration of normal wear and tear and in the repair of injuries to the V.E.M.'s in arteries.

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SARCOMA ARISING IN OMENTAL ENDOMETRIAL CYST

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The behavior potential of the adult celomic epithelium and mesenchyme, largely restricted to the female pelvic area, is expressed not uncommonly in such tissue reactions as endometriosis and decidua formation. Its capacity for neoplasia, however, except in relation to such already differentiated and complex organic structures as those of the female genital tract, is slight. Thus, as is well known, primary tumors whether of the peritoneal layer itself or arising within foci of endometriosis are exceedingly rare. Corner, Hu and Hertig (1) found only eight reported cases showing satisfactory evidence of carcinoma arising in endometriosis, to which they added three of their own, all eleven occurring within the ovary, and did not mention the occurrence of sarcoma. Ober and Black (2) were able to find only three instances of sarcoma arising within the pelvic supporting tissues outside the uterus, two of these three cases forming the basis of their report; in one of the two cases there was a para-uterine tumor which presented the histologic composition of endometriosis with areas of sarcomatous transformation. The case reported here is an uniquely unequivocal example of sarcomatous transformation of the stromal component of an already distinctive and entirely extra-uterine and extra-adnexal endometriotic lesion.

REPORT OF THE CASE

The patient was a 44 year old single white female who had been well until two weeks before admission when she suddenly experienced sharp pain localized within the lower abdomen. The pain lasted for about an hour, and subsided after an injection by her physician. It recurred the next day although less intense and localized more to the right side, and there was also slight fever. Past and menstrual history were essentially negative; patient's menstrual cycles were regular, 26 days, and the menses were of average duration and amount. The episode of pain occurred on the first day of her last menstrual period which was otherwise normal. Several days later a mass was felt within the right lower quadrant of the abdomen. Gastrointestinal x-ray series was reported as negative. During the next week patient felt well except sometimes for slight pain in the right lower quadrant on standing up. On admission to hospital, physical examination revealed a well nourished and well developed adult white female showing nothing noteworthy externally. There was some 'guarding' on palpation of the lower abdomen, where a large although ill-defined tumor was felt, more on the right side. Laparotomy revealed a large tumor firmly attached to and receiving

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its blood supply from the greater omentum. It was entirely outside the pelvis and apart from the uterus and adnexa. The uterus was enlarged by fibroids. There were hemorrhagic fibrous adhesions over the serosal aspect of the uterus, adnexa and appendix. Total hysterectomy, appendectomy and excision of the omental tumor were performed.

Pathologic Findings

Gross. The omental tumor was fluctuant and of irregularly lobulated external contour. It measured approximately 15 to 20 cm. in diameter. On section, it proved to be cystic in structure. Most of the cyst wall averaged 2-3 mm. in thickness, and was of slightly soft consistence and grayish color. In one area the cyst wall expanded to 8 cm. in width, and was of grayish to yellowish-tan color, and distinctly myxomatous appearance and consistence (Fig. 1). The inner lining of the cyst was smooth and irregularly trabeculated, and the cyst space was occupied by thin brownish fluid. The uterus was enlarged by a number of fibroids. Its serosal surface was generally smooth but presented a few hemorrhagic fibrous adhesions. There were numerous similar hemorrhagic fibrous adhesions over the serosal aspect of the tubes, ovaries and appendix which were otherwise not noteworthy. One of the ovaries contained a recent corpus luteum.

Microscopic. Sections through the thin portion of the cyst wall, which comprised the major portion of the cyst, showed it to be composed throughout its width of endometrial glands and stroma of much the usual histologic appearance. In some areas the glands were of normal size, tubular or variably coiled, and composed of the usual columnar epithelium, occasionally ciliated, for the most part pseudostratified, in areas showing subnuclear vacuolization (Fig. 4). In other areas there was an intermingling or even predominance of glands showing moderate to considerable microcystic dilatation associated with flattening of the



FIG. 1. Part of the large omental endometrial cyst, after opened and sectioned, showing the cyst space with smooth irregularly trabeculated lining, the thin endometrial part of the cyst wall, and the relatively abrupt expansion of the latter into the myxosarcomatous portion. (Ruler is 10 cm. length.)

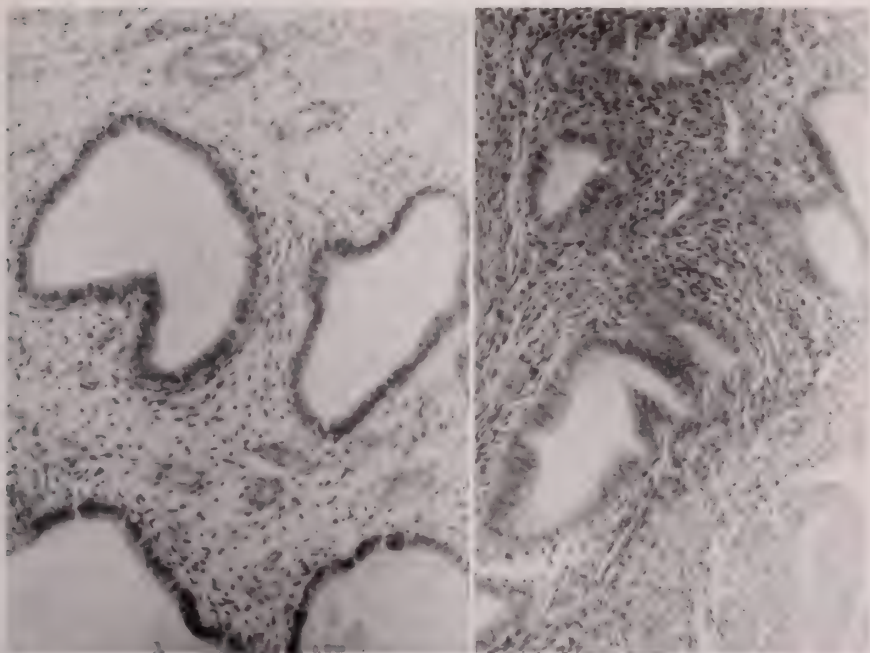


FIG. 2. Composite of two areas of the endometrial cyst wall. On the left the stroma is edematous and the glands show subnuclear vacuolization, as in the early secretory phase; on the right the stroma is compact and the glands resemble those of the endometrium in the proliferative phase ($\times 120$).

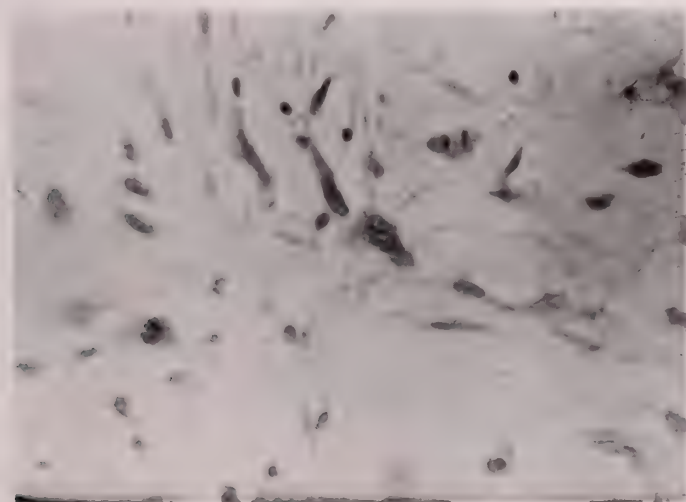


FIG. 3. Field from the wide myxosarcomatous portion of the cyst wall showing marked cytologic atypism, basophilic interfibrillar ground substance, and atypical mitotic figures ($\times 430$).

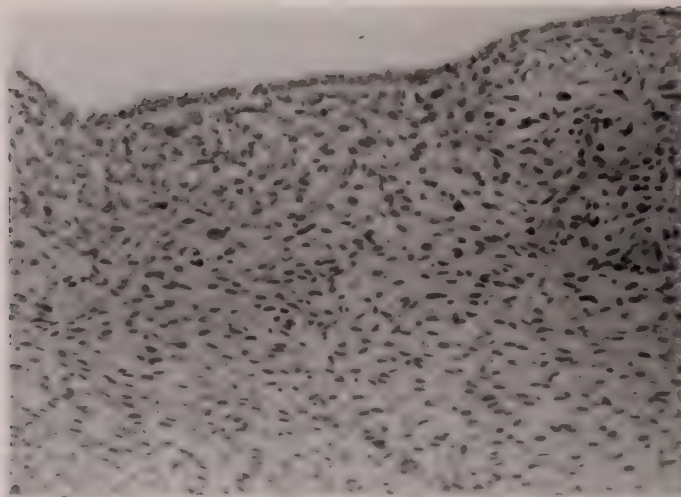


FIG. 4. Area of cyst wall showing zone of marked cytologic atypism adjacent to inner lining ($\times 120$).

lining epithelium. Some of these cystic glands were of decidedly irregular contour. Throughout, the cyst was lined on its inner surface by a layer of columnar epithelium, similar to that of the normal uterine endometrium (Fig. 2), while the external surface was bordered in part by a layer of small flat or cuboidal epithelium of mesothelial character, in places with an attached narrow layer of tissue of loose granulation tissue structure; in other areas this was replaced by a relatively narrow band of fibrous tissue. Much of the stroma was more or less compactly cellular, resembling the lamina propria of the uterine endometrium. The stromal cells presented the usual small round or oval vesicular nuclei with uniform fine reticulated chromatin network, negligible cytoplasm, and associated delicate meshwork of fibrillar reticulum. Dispersed throughout were numerous thin or moderately thick-walled small blood vessels. As the cyst wall widened, the stroma in places assumed an edematous or myxomatous appearance. There was a spreading apart of the delicate fibrils, and in places a faintly stained, slightly basophilic interfibrillar ground substance could be observed but for the most part the interstices appeared empty. This change was accompanied by flattening and elongation of the nuclei toward a spindle shape. In a few areas, there was a slight tendency to a fascicular arrangement of the cells associated with more collagenous character of the fibers.

A conspicuous histologic feature in some sections as the cyst wall expanded was the presence beneath the inner lining (see Hertig's comment below) of a zone of striking histologic change, with relatively abrupt transition to the remainder of the wall still histologically constituted as described above. In this zone, which was of moderately but not closely compact cellularity, the nuclei were largely oval, much larger, and of more coarse hyperchromatic structure. There was some variation in size, with occasional giant or multiple nuclei, irregularity in shape and numerous scattered mitotic figures. Occasional large bizarre hyperchromatic nuclei were present. There was slight to moderate spreading of

the intercellular fibrils, and a faintly visible interfibrillar ground substance in areas, in other areas none. The latter change and the cellular atypism tended to increase toward the thick portion of the cyst wall where it assumed, moderately abruptly, a striking myxomatous appearance. In this part of the cyst wall, some areas of non-neoplastic endometrial glands and stroma remained; most of this portion of the cyst wall was of distinctive myxomatous histology (Fig. 3): there were ill-defined bundles and whorls of spindle or stellate cells, with widely separated fine to moderately coarse fibrils and variably prominent basophilic interfibrillar ground substance. The nuclei showed pleomorphism and atypism, and there were numerous scattered mitotic figures, some of atypical character. In this myxomatous portion of the cyst wall, the glands were considerably diminished in number and in places there were few or none. The remaining glands tended to be cystic and lined by flattened epithelium. There were occasional interspersed areas of much less altered endometrial histology, composed of non-neoplastic glands and stroma or glands surrounded by stroma showing much less cytologic atypism. One section contained an area comprised of moderately defined bundles of spindle cells of fibroblastic type showing considerable nuclear atypism, and associated fibers of more collagenous character. This area had the appearance of the ordinary fibrosarcoma. Sections stained by the trichrome, Mallory's phosphotungstic acid-hematoxylin, and Wilder's silver methods brought out the loose stromal meshwork of fine to moderately coarse reticulum fibers surrounding the stromal cells. No significant differences in the composition and texture of the fibers were noted between the non-neoplastic and neoplastic areas except that where there tended to be a fascicular arrangement as described above, the reticulum fibers tended to assume a similar pattern. Other sections showed extensive foci of endometriosis of the uterus and adnexa, and a recent mature corpus luteum of the ovary. The uterine endometrium was of ordinary histologic structure with subnuclear vacuolization of the endometrial glands characteristic of the early luteal phase.

COMMENT

Of particular interest was the clear-cut sarcomatous histologic transformation of the stromal component of the cyst wall. Much of the latter was composed diffusely of endometrial glands and stroma of ordinary histologic appearance. This merged through an intervening zone of myxomatous change of the ground substance of the stroma with an area characterized by diminution or disappearance of the endometrial glands, and neoplastic change of the stromal cells characterized by striking nuclear pleomorphism, irregularity of size and shape, hyperchromatism and numerous scattered atypical mitotic figures. This myxomatous feature also characterized many of the cases of sarcoma of the endometrial stroma, designated as fibromyxosarcoma, in the series reported by McDonald, Broders, and Counseller (3), although it was not conspicuous in three such cases previously studied by one of us (AMG). The only other example of sarcomatous change of the stroma in endometriosis that we have been able to find is Case 2 of Ober and Black, and questionably Case 1 of Ober and Jason (4). With respect to the present case, Novak (5) stated that this was the only instance of this par-

ticular type of malignant change in an endometrial cyst which he had seen, and Hertig (6) commented that "this is a most fascinating case, firstly because it appeared to be completely separate from the uterus and adnexa, and secondly because of its histologic pattern. This sarcoma of the endometrial stroma is unique in my experience since it shows the origin from the so-called cambium layer just beneath the surface. This is sometimes a prominent feature in sarcoma botryoides and is the layer from which this tumor is said to arise."

The unequivocal sarcomatous change of the stromal component of an ectopic endometriotic lesion was but one, albeit the most important, of a number of features of interest presented by this omental tumor: its strikingly large size, its development in the form of a thick-walled and smooth-lined cyst, the distinctive endometrial histologic structure of much of the cyst wall, and its entirely extra-uterine and extra-adnexal location. Leffler (7) also reported a small omental cyst which resembled the present lesion in being composed of endometrial glands and stroma; in addition it included a layer of smooth muscle suggesting myometrium, which was considered by the author as supportive of the hypothesis of celomic mesodermal differentiation in the histogenesis of this instance of endometriosis since there would be no muscle included in an endometrial implant. We believe that the location of the present large omental endometrial cyst, outside the pelvis and genital tract, with the coincidental formation of ordinary foci of endometriosis of the latter tissues, similarly speaks for the role of the celomic mesenchyme in its histogenesis. The importance of the latter tissue in the origin of endometriosis generally finds logical support from its embryologic relationship to the uterine endometrium which itself derives from the Müllerian duct and associated celomic mesenchyme.

SUMMARY

The rare, almost unique, occurrence of sarcoma arising in the stromal component of a large omental endometrial cyst is described. This distinctive endometriotic lesion arose entirely away from the internal genitalia, coincidentally with ordinary endometriosis of the latter. It is suggested that this lesion may represent an unusually distinctive manifestation of the proliferative capacity of the celomic mesenchyme, and that the latter plays a fundamental role in the genesis of endometriosis.

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PEPTIC ULCER IN GALL BLADDER DIVERTICULUM

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Congenital anomalies of the gall bladder are uncommon (1). Recorded cases of differentiated gastric mucosa in the gall bladder are few. Egedyi (2) described a papilloma consisting of heterotopic gastric epithelium including chief and parietal cells in 1934. Pessel et al (3) reported a crateriform mural lesion containing chief glands in 1950 in a man 23 years old. Williams and Humm (4) reported an intramural nodule containing gastric corpus mucosal glands in 1953 in a man 28 years old and McKibben and Hall (5) a similar nodule in 1954 in a woman 53 years old. Peptic ulceration was not found in these heterotopic areas.

CASE REPORT

N. B., male, white, 16 years of age was admitted to the surgical service of Dr. Max Miller on November 1, 1944 complaining of intractable right upper quadrant pain. In March 1943 he first began to suffer dull right upper quadrant pain which awakened him from sleep, radiated to both groins, persisted for a half to one hour and gradually subsided spontaneously. There was no nausea or vomiting. His appetite was good. A physician was consulted and an appendectomy performed. Convalescence was uneventful and he remained symptom free for two months. Thereafter he experienced severe epigastric pain, ten minutes after eating, which 'doubled him up' and radiated to the sternum and both costal margins. Episodes of pain were followed by symptomless intervals. Each recurrence was however characterized by pain of greater intensity and longer duration until one month before hospitalization when the pain again began to awaken him and remain for six to eight hours. He lost ten pounds. There was no nausea, vomiting or jaundice. A gall bladder series showed gall bladder dysfunction. No calculi were seen. At operation the gall bladder was without significant gross change and was covered by smooth serosa. No abnormalities were encountered during the cholecystectomy.

Gross examination

The gall bladder received in fixative measures 8.5 cms. in length by 2 cms. in diameter and is resected through the cystic duct which measures 2 mms. in diameter. The gall bladder bed is covered by a small amount of shaggy tissue. The serosa is smooth. The lumen contains thick, viscid, colorless fluid. There are no calculi. The mucosa presents fine interlacing ridges and is grey except for greenish discoloration near the cystic duct. The wall measures 1 to 2 mms. in thickness. At the junction of the ampulla with the cystic duct the lumen is narrowed by a firm thickening within the serosal aspect of the gall bladder wall. On section through this region there is an intramural loculus (Fig. 1) 1 cm. in diameter connected with the main lumen through a narrow channel whose ostium is proximal to the site of narrowing. The loculus is lined by granular greenish tissue. Within the subserosal tissue adjacent to the loculus there is a lymph node 1 x 0.8 x 0.3 cm.

From the Laboratories of Christ Hospital, Jersey City, N. J.

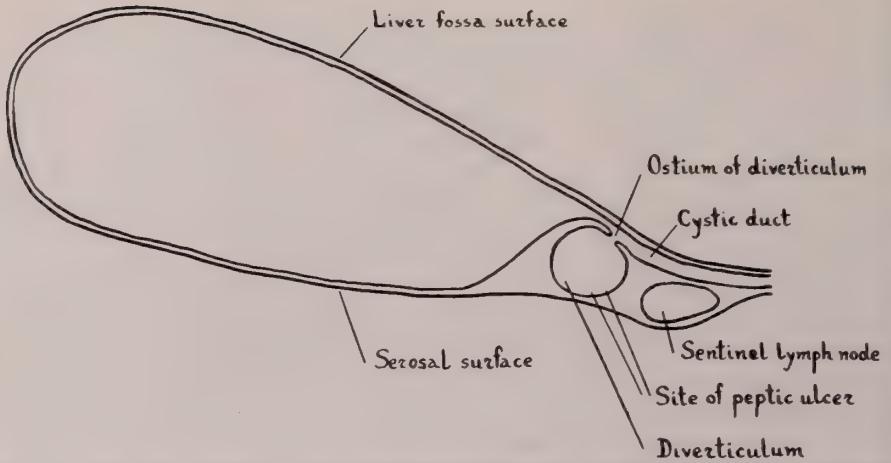


FIG. 1. Schematic drawing of the Gall Bladder showing location of intramural diverticulum within serosal aspect of wall at the neck. The peptic ulcer is in the deep portion adjacent to the serosa.

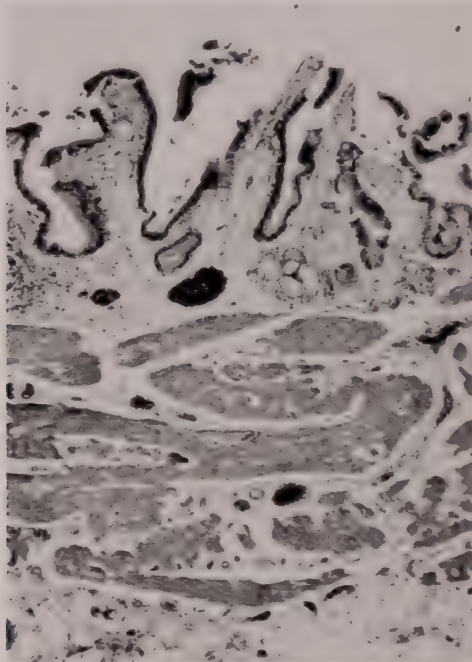


FIG. 2. Corpus of Gall Bladder ($\times 80$)—Wide villi. Tubulo-alveolar glands. Widened muscularis traversed by fibrous tissue.

Microscopic examination

Fundal and ampullary portions of the gall bladder. The villi forming the interlacing ridges seen grossly are wider (Fig. 2) than usually seen in the gall bladder and covered by pseudostratified columnar epithelium with basophilic finely

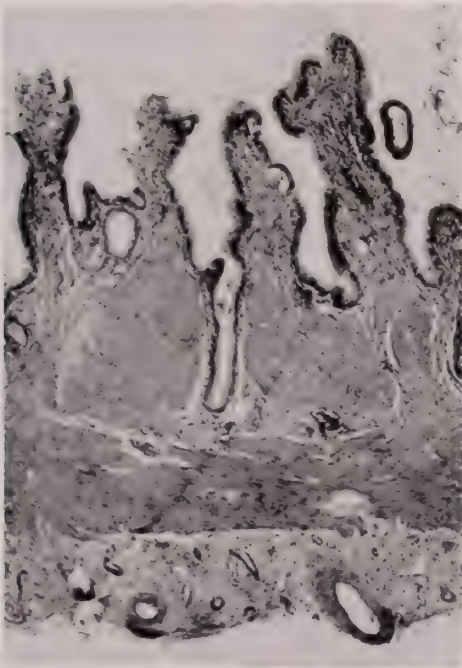


FIG. 3. Corpus of Gall Bladder ($\times 80$)—Hypertrophied muscularis. Muscle bundles in bases of villi. Deep crypt lined by surface cells (Aschoff-Rokitansky sinus).

granular or basally vacuolated cytoplasm. The apical cytoplasm of many of the cells contains faint, very small brownish pigment granules. The nuclei vary in size and shape and in their location in the cell, some being situated almost at the cell surface. The basement membranes are thickened and in places unclear.

The stroma of the villi is composed of fine and dense collagenous fibers. Stromal cells are prominent. There is scattered infiltration by lymphocytes, small numbers of eosinophiles and an occasional plasma cell.

In some portions of the wall the surface epithelium becomes continuous with small glands lined by cuboidal cells with apical neutrophilic or eosinophilic cytoplasm and basal flattened nuclei (Fig. 2). In other scattered areas the surface epithelium is continuous with crypts (Fig. 3) that extend into the muscularis and serosa and form dilated acini with wavy walls. Those in the serosa are surrounded by cellular fibrous tissue infiltrated by lymphocytes.

The muscularis is dense and wider than usual. Some smooth muscle bundles project into the stroma of the bases of the villi (Fig. 3). Stromal fibrous tissue with basophilic matrix extends between the muscle bundles and follows the epithelial pits into the muscularis and serosa (Fig. 2).

The serosa is wide and contains congested veins and capillaries and nerves.

Area of intramural locus at the gall bladder-cystic duct junction. Near the ostium of the locus the villi are wider and form interlacing bridges. The stroma is more heavily infiltrated by lymphocytes and plasma cells and contains glands even in the apical portions. The glands occupy the major portion of some of the

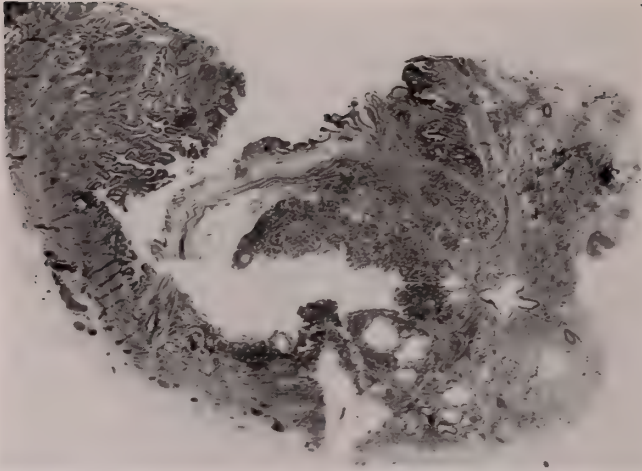


FIG. 4. Intramural Diverticulum ($\times 8$)—Note numerous glands in lamina propria that extend to the mucosa of the diverticulum (especially on right); dilated pits and irregular architecture; dilated pits in serosa.

villi, leaving but little stroma, and are continuous with numerous glands in the wall (Fig. 4).

These glands replace the muscularis and extend into the serosa and to the mucosal lining of the loculus. Fibrous tissue and smooth muscle bundles are between groups of glands and in places separate these glands from the mucosal lining of the loculus.

The cells which line the villi near the loculus ostium consist of basophilic columnar cells like those described in the fundal and ampullary portions of the gall bladder and interspersed tall goblet cells, very numerous at the ostium. As the distance from the ostium increases these cells become less numerous and disappear. The goblet cells contain unclear eosinophilic granular and smooth material enclosed by a dense narrow rim of cytoplasm. The contents of some of the goblet cells project into the gall bladder lumen through defects in the apical cytoplasm. A few scattered columnar cells are more coarsely granular, more deeply eosinophilic and resemble Paneth cells.

The summit of the wall of the loculus that borders on the gall bladder is thin (Fig. 1). On the gall bladder aspect the surface is flat and marked by a few low folds. The surface cells are mainly goblet cells. The underlying stroma contains glands of antral type with scattered goblet cells. The stroma is loosely fibrillar and is infiltrated by lymphocytes and plasma cells. Several narrow smooth muscle bands separate this mucosal surface from the mucosa of the loculus composed of gastric surface epithelium and short peptic glands with necks bordered by mucous and acid cells and deeper portions composed of peptic (chief) cells and acid (parietal) cells (Fig. 5). The peptic glands are separated by loose fibrillar stroma infiltrated by lymphocytes and plasma cells and by dilated pits lined by epithelium of gastric surface type.

Intramural loculus—is lined by epithelium of surface gastric type beneath

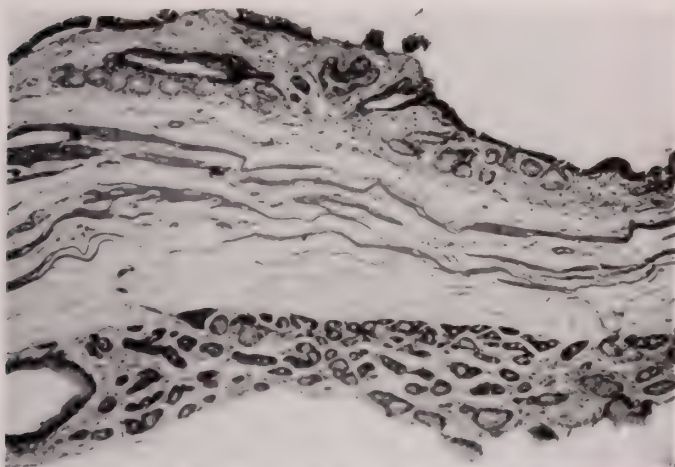


FIG. 5. Gall Bladder Lumen Aspect of Diverticulum ($\times 60$)—Note goblet cells lining lamina propria and crypts (at upper border of photomicrograph). Tubulo-alveolar glands. Mucosa of gastric corpus type lines diverticulum (along lower border).

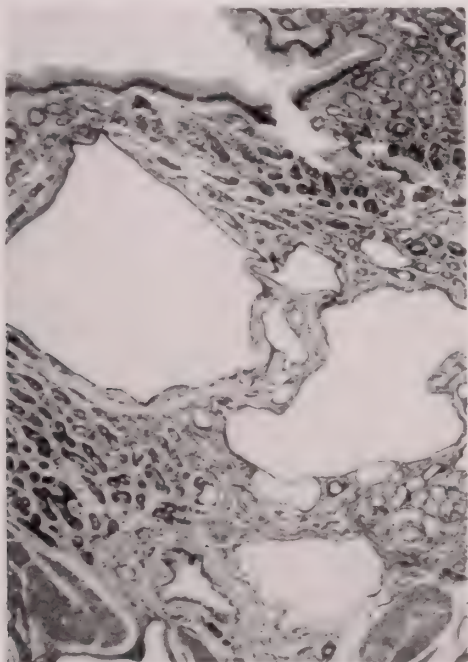


FIG. 6. Diverticulum Wall ($\times 80$)—Mucosa of gastric corpus and (lower right) transitional zone type. Dilated pits, muscle bundles and increase in stroma.

which there are peptic glands in the vicinity of the ostium and antral and eosinophilic prepyloric glands in the distal portions of the loculus. Between these regions the mucosa of the loculus contains glands composed of mucous, peptic and acid cells (Fig. 6) or only mucous and acid cells interspersed among mucous and prepyloric glands as seen in the transitional zone of the stomach.

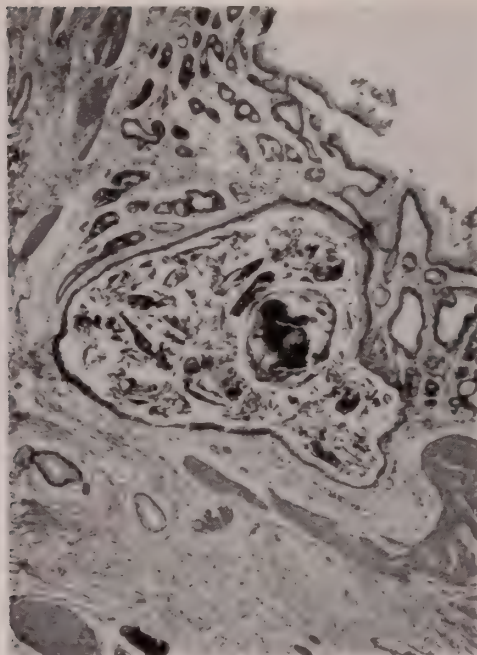


FIG. 7. Diverticulum Wall ($\times 80$)—Mucosa of gastric corpus type. Dilated pit containing bile pigment. Smaller pits lined by gastric surface cells external to muscle.

The architecture in all portions of the locus is moderately distorted by the relatively large amount of interglandular stroma, scattered cystic pits, in places numerous and closely approximated, and scattered wide and narrow bands of smooth muscle which traverse the stroma between the mucosal lining and the serosa and between groups of glandular structures (Fig. 6). In the fibrous tissue external to the muscle bundles cystic pits often associated with glandular formations lie within moderately dense fibrous tissue or basophilic myxoid fibrous tissue (Fig. 4).

The cystically dilated pits contain granular, greenish-brown bile pigment, pink granular material and desquamated degenerating cells (Fig. 7). The lining cells are of surface gastric type with eosinophilic apical cytoplasm. In many however the lining cells are flattened or absent.

In the region of the ostium the tall eosinophilic surface cells are continuous with short pits (except for those which penetrate for variable distances to form the cystic dilatations) and necks lined by mucous and acid cells and the more numerous branching peptic or chief glands lined by peptic (chief) and acid (parietal) cells. No argentaffine cells are found in this portion of the locus. The architecture in this portion resembles the late fetal stomach in that there is separation of the glandular elements by relatively larger amounts of stromal tissue and earlier branching of the glands than is seen in the adult stomach. The stroma is moderately infiltrated by lymphocytes, plasma cells and some eosinophiles and Russell bodies.

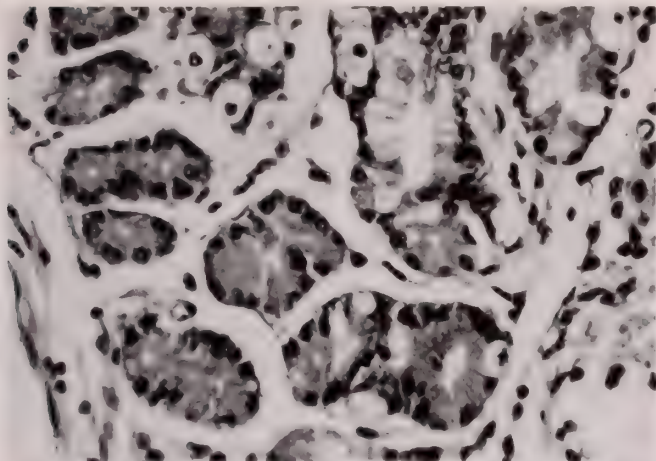


FIG. 8. Diverticulum ($\times 600$)—Mucosa of corpus type. Note granular peptic cells and oval parietal (acid) cells. Mucous neck glands at upper right.

The mucous cells of the necks (Fig. 8) and the antral type glands are cuboidal or pyramidal with neutrophilic or eosinophilic cytoplasm that is faintly granular or marked by cytoplasmic strands with intervening clearer areas and basal nuclei.

The peptic cells are pyramidal and contain numerous small basophilic cytoplasmic granules. Their nuclei vary in size and staining intensity (Fig. 8).

The acid cells are oval or round with pink cytoplasm and central or eccentric nuclei (Fig. 9). Some present clear channels in the cytoplasm as seen in secretory activity; others are vacuolated. In the acini composed of mucous and acid cells the parietal cells reach the lumen. In the acini composed of peptic and acid cells the parietal cells do not reach the lumen. Channels between the peptic cells lead to the acid (parietal) cells. Some of the acid cells contain two, a few three nuclei.

Most of the glands are demarcated from the stroma by thin basement membranes. Some of the acini contain degenerating peptic and acid cells with shrunken cytoplasm or vacuolization of the peptic cell cytoplasm. Nuclei in these are pyknotic or as in the acid cells barely visible. Their basement membranes are unclear so that the cells merge with the stroma.

At the distal end of the loculus there are closely approximated mucous glands of prepyloric type lined by tall cuboidal cells with eosinophilic cytoplasm and basal flattened nuclei and antral mucous glands (Fig. 10). Some argentaffine cells are between the bases of these cells. The glands are separated only by their basement membranes or small amounts of stroma. Among them there are dilated pits surrounded by dense collagenous tissue and looser stroma infiltrated by plasma cells. On one side peptic glands are scattered among the mucous prepyloric glands (transitional zone). Degenerating mucous and peptic glands are within the stroma around the dilated pits.

The stroma beneath the surface cells is edematous and infiltrated by plasma cells and lymphocytes, some of which also infiltrate the basal portions of the

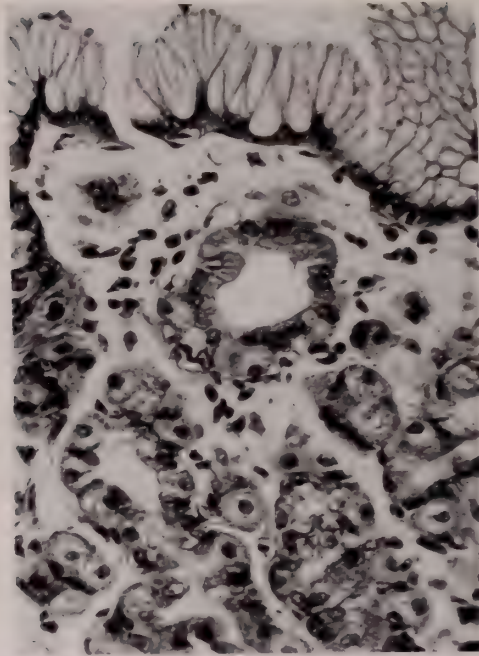


FIG. 9. Diverticulum ($\times 600$)—Mucosa of corpus type. Typical acid cells with clear zones in cytoplasm. Note cells in stroma.

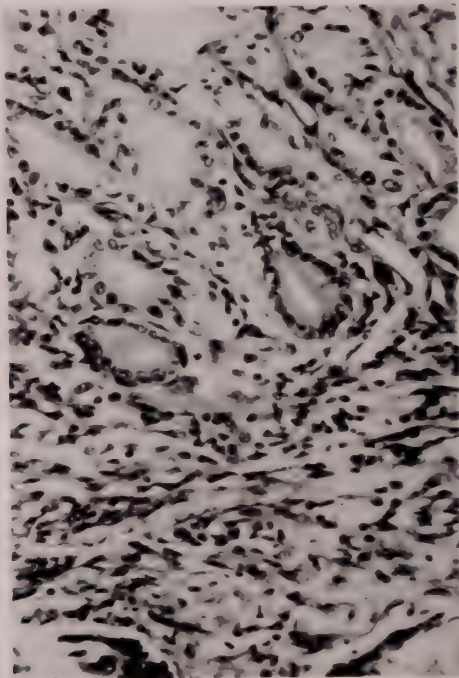


FIG. 10. Diverticulum ($\times 400$)—Mucosa of antral type - antral glands. Moderate infiltration basally.

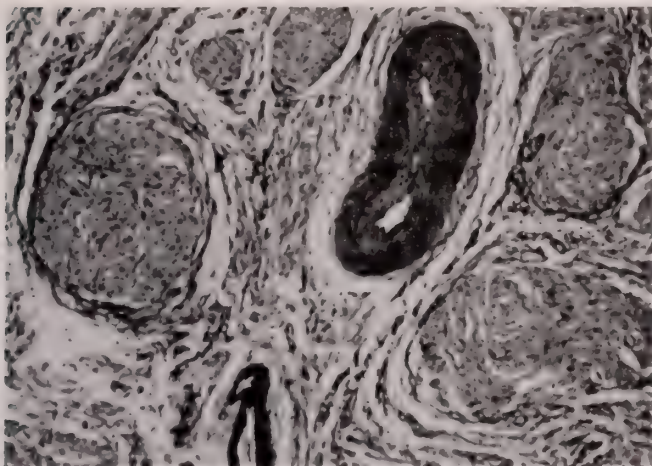


FIG. 11. Diverticulum ($\times 120$)—Serosal wall in antral portion near ulcer—Note many nerves. Intimal widening of artery.

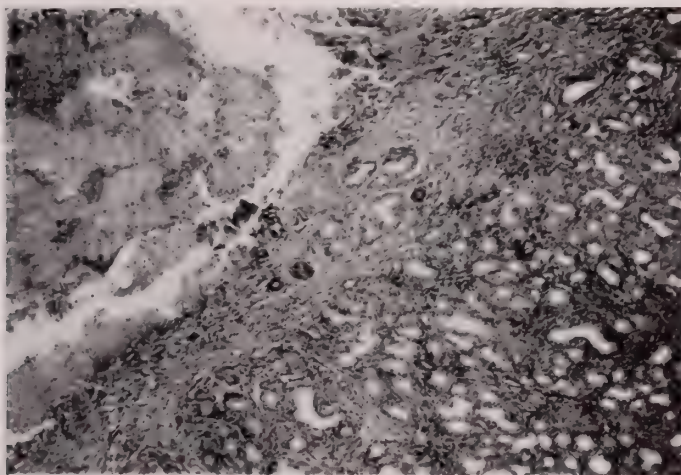


FIG. 12. Diverticulum ($\times 100$)—Peptic ulcer in antral portion—Note glands of gastric antral and few of prepyloric type, peptic digestion and reaction in ulcer base.

surface cells. There are lymphoid aggregates in the deeper portions of this antral mucosa.

The deeper zone of mucous glands is traversed by smooth muscle bundles which separate groups of glands and the lumen of the loculus from cystic pits between the muscle and the serosa. Groups of glands lie within stromal septa in the muscle bundles. The subserosal stroma of this region of the diverticulum contains numerous nerves (Fig. 11) some basophilic and myxomatous.

The ulceration involves the distal portion of the loculus lined by mucosa of antral and prepyloric type (Fig. 12). The glandular elements and muscle bundles on the serosal aspect are no longer present and replaced by the ulcer base which penetrates the wall (Fig. 13). On the gall bladder lumen aspect the ulcer base

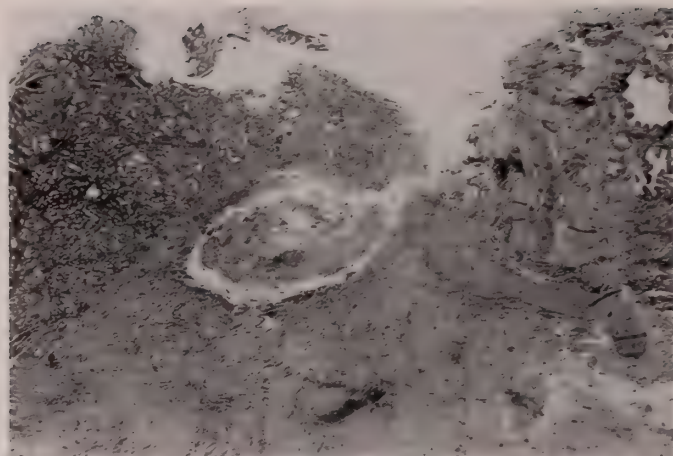


FIG. 13. Diverticulum ($\times 10$)—Peptic ulcer—Replacement of glands and muscle in ulcer base by reactive fibrous tissue. Note large nerves in ulcer base and numerous antral type glands on gall bladder lumen aspect (on left).

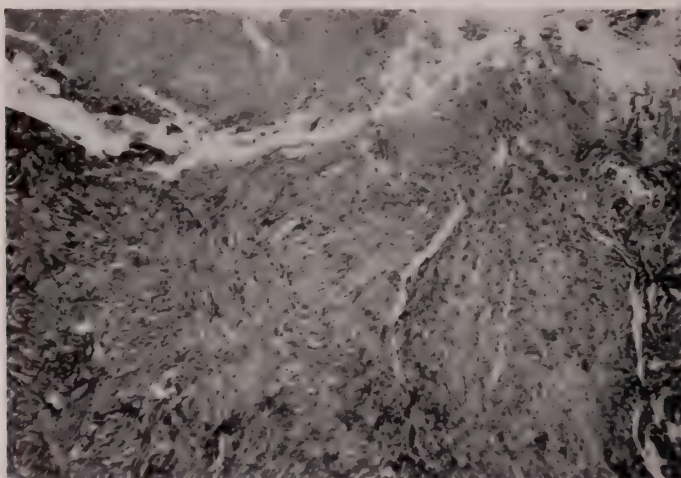


FIG. 14. Diverticulum ($\times 100$)—Peptic digestion of nerves in ulcer base. Cellular infiltration.

is formed by altered collagenous tissue distally and proximally (toward the ostium) by antral glands which merge with glandular acini beneath the mucosal folds of the gall bladder (Fig. 13). The ulcer is filled with fibrin, eosinophilic granular material (precipitated serum), some polymorphonuclear leucocytes and poorly staining cells and nuclei undergoing peptic digestion (Figs. 12, 13). The ulcer floor is formed by cellular, fibroblastic tissue which contains many capillaries, nerves and fragmented glands. Several large nerves in the ulcer floor present eosinophilic swelling with obliteration and separation of fibers and myxomatous alteration (Fig. 14). Deep to this zone there is denser collagenous

tissue that contains numerous nerves and is infiltrated by lymphocytes and some polymorphonuclear leucocytes, eosinophiles and plasma cells. The intima of arteries within this tissue are moderately widened. A few small veins contain eosinophilic, smooth (fibrin) thrombi. This tissue separates the ulcer floor from the serosa. There is no serosal reaction.

COMMENT

The intramural nodule described by Williams and Humm (4) was 2 cms. in diameter, freely movable into the lumen of the ampulla, non-encapsulated and within the subserosal tissue of the neck of the gall bladder. It was composed of cystically dilated pits, chief glands and irregularly arranged smooth muscle bundles. The nodule reported by McKibben and Hall (5) was approximately 1 cm. in diameter, non-encapsulated and situated in the deeper portions of the mucosa of the neck partially surrounded by muscularis. It contained surface gastric lining cells, pits and mucous and chief glands. There was no connection with the lumen of the gall bladder in either case. The aberrant gastric mucosa reported by Egedyi (2) occurred in a papilloma at the neck. The ectopic focus of Pessel et al (3) was likewise located in the neck region and contained chief glands lined by peptic and acid cells depicted in the photomicrographs. Peptic ulceration was not found in any of these cases.

In the present instance the heterotopic gastric mucosa was situated in a non-encapsulated intramural diverticulum within the serosal aspect in the neck region connected with the gall bladder lumen through a small ostium. The diverticulum was lined by typical tall eosinophilic gastric surface lining cells and presented mucosa of gastric corpus type near the ostium separated from mucosa of antral prepyloric type by mucosa of gastric transitional zone type. The cystic dilatations were lined by gastric surface and pit epithelium. Degenerative changes seen in the peptic and acid cells were also observed by McKibben and Hall (5). The architectural pattern of the diverticulum is that of a miniature stomach in the gall bladder wall with irregular glandular, stromal and muscle relationships. The deep portion of the wall lined by antral mucosa contained numerous large nerves.

Acquired diverticula of the gall bladder are not infrequently encountered in association with chronic cholecystitis (6). They occur in the body and fundus, are lined by gall bladder surface cells which project into or through the muscularis and are occasionally bordered by glandular acini. These outpouchings at times contain calculi and may fill with dye during cholecystography (7). Congenital diverticula are rare. Gross (1) in a review of 148 congenital anomalies of the gall bladder collected from the literature found nine diverticula, five demonstrated roentgenographically, and believed them to be 'closely related to the development of the cysthepatic ducts' which course between the neck of the gall bladder and the adjacent liver related to the gall bladder fossa. He explained the presence of the diverticula on the serosal (exposed) surface of the gall bladder by the 'normal rotation' of this organ. He states that histologic studies were not

available. Those situated on the serosal aspect projected beyond the silhouette of the gall bladder. This diverticulum was situated entirely within the gall bladder wall and could not be appreciated on external examination. A thickening was however palpable within the serosal aspect of the gall bladder wall in the neck region.

The peptic ulceration involved the deeper portion of the diverticulum lined by mucosa of gastric antral type as is common in the stomach. The ulcer cavity contained desquamated digested debris, cells which showed the usual alteration of peptic digestion and a moderate number of inflammatory cells. The peptic digestion caused almost total disappearance of glandular elements in some areas and extensive erosion of some of the many nerves in this portion of the wall. The inflammatory reaction was moderate and the reactive fibrosis similar to that seen in a peptic ulcer base. The serosa was not involved.

It is of interest to note that the two previously reported nodules (4, 5), the ectopic gastric glands reported by Pessel et al (3), the papilloma reported by Egedyi (2), the chloride secreting papilloma reported by Kerr and Lendrum (8) and the gastric diverticulum of this case were all located in the neck region of the gall bladder at or near the cystic duct-gall bladder junction. Embryologically the gall bladder arises from the caudal portion of the hepatic diverticulum (1, 9). What relationship this bears to the location of the ectopic foci in the gall bladder neck is not clear. The duplication of the stomach pattern in this case suggests that the displaced anlage from which the diverticulum arose was composed of developmentally determined cells (9). There is histologic evidence of functional activity of both the acid and peptic cells. Argentaffine cells were present in the antral glands.

No other anomalies were recorded in any of the reported cases. Goblet cells, which do not occur in the gall bladder (10), were found by Kerr and Lendrum (8) only in the chloride secreting papilloma. There were none in the lining epithelium of the remainder of the gall bladder. In the present case goblet cells lined the lamina propria adjacent to and for some distance from the ostium of the diverticulum. The corpus and fundus contained tubulo-alveolar glands not ordinarily present in the lamina propria except in the region of the neck (6, 10) and at times associated with cholecystitis. The mild inflammatory reaction in this gall bladder was not considered sufficient to explain the occurrence of these glands which involved the entire gall bladder wall adjacent to some portions of the diverticulum and were associated with papillary formations on one side of the ostium. Muscle bundles occupied the bases of the villi as seen in the valves of Heister (10).

The gall bladder lumen was narrowed at the neck by the intramural ectopic gastric tissue so that colorless, viscid fluid occupied the lumen. Bile pigment which discolored the mucosa of the diverticulum and was found in the dilated pits entered through the ostium situated proximal to the site of narrowing. Nevertheless the diverticulum was not visualized by cholecystography. The hypertrophy of the muscularis of the gall bladder was considered due in part to the narrowing at the neck.

SUMMARY

A peptic ulcer in an intramural diverticulum of the gall bladder lined by gastric corpus and antral mucosa is described. The histology is emphasized.

Four previously reported cases of ectopic gastric mucosa in the gall bladder are reviewed.

No other case of peptic ulceration of ectopic gastric mucosa in the gall bladder could be found in the literature.

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PATHOLOGICAL CHANGES AFFECTING THE NUCLEAR CONSTITUENTS: CYTOCHEMICAL STUDIES

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INTRODUCTION

It is a basic tenet of cellular pathology that the cell is the unit of disease. In drawing attention to the cell in disease, Virchow was referring to the cell as a chemical unit into whose processes and their disturbances it was the aim of scientific pathology to inquire. This objective is best served when details of both structure and composition can be interrelated, spatially and temporally, in health and in disease. The advent within less than twenty years of powerful new technical modalities for the elucidation of cell structure, constitution and localization of components, in addition to the refinement of older methods for studying cell behavior, have brought about a great expansion of our information about the biology of the cell. This newer knowledge and its methodology promises to lay the foundation for the development of a truer pathology of the cell, such as was envisioned by the founder of the cellular pathology a century ago.

Although morbid appearances of structural and tinctorial alterations of cells as seen with conventional methods have been carefully documented (1, 2), and biochemistry has contributed abundantly toward elucidating metabolic disorders, chemical study of the constitutive components of the cell in disease is mostly of rather recent development. In some part this lag is due to the requirement imposed by the necessity of localizing specific substances in individual cells in tissues, and within the cell. Even parenchymatous tissues such as liver are remarkably inhomogeneous not only with respect to cell type and physiological state of their constituent cells, but especially in relation to lesions, which are often focal or zonal, and in different stages of evolution. The performance of such analyses lie within the province of histo- and cytochemistry and the extra situm separation methods of cell chemistry, carried out with microscopic control.

Most recent studies of the cell in disease have focussed on changes in the cytoplasm and its constituents, investigations which because of the many methods of microscopic histochemistry, electron microscopy and differential centrifugation applicable to them, have been numerous. There have been fewer such descriptions of morbid processes affecting cell nuclei. However, in situ methods for the chemical determination of the constituents of nuclei that are both qualitative and quantitative are available. These include specific staining reactions, microspectrophotometry in the ultraviolet and visible range, radioautography, fluorescence microscopy with fluorochrome labelled materials and interferometric microscopy. The cytochemical studies presented in this communication that

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have been carried out in the Histochemistry Research Laboratory have chiefly employed dye-binding reactions and microspectrophotometry. In the following paragraphs the principal chemical components of the cell nucleus and some of their properties will be described together with those histochemical methods for their demonstration *in situ* which lend themselves to quantitation, and a brief review of how these substances may be measured.

CONSTITUENTS OF THE CELL NUCLEUS AND SOME HISTOCHEMICAL METHODS FOR THEIR QUANTITATIVE DETERMINATION

Chemical analysis of the materials composing the interphase nucleus has been made more accurate by methods permitting the isolation of nuclei in non-aqueous media (3) and the preparation of "chromosomal" threads (4). The properties and metabolism of these substances have been studied with a variety of methods.

1. Highly polymerized deoxyribonucleic acid (DNA) is a constituent of the chromosome and the principal basophilic material of the nucleus. It exhibits the constancy of composition (5) and amount per cell (6-8), and the correlation with genetic change (9, 10) of a genetic determinant, and for this reason DNA is frequently referred to as the hereditary material. Its low uptake of radioisotopes in the non-dividing cell shows DNA to be among the most stable substances in the cell; incorporation of isotopic precursor (11, 12), which occurs in interphase (13), is correlated with premitotic DNA synthesis (14). Determination of the content of DNA per nucleus in a variety of differentiated tissues in many species discloses that the relative amounts measured fall into clearly defined classes whose means are in a geometric (1:2:4) ratio (15-20). The ratio between the mean amount of DNA in diploid somatic and in haploid sex cells is 2:1 (referred to as 2C' and 1C' classes) (16-20) and the amounts of DNA in a population including polyploid cells, such as those in mammalian liver, occur in definite geometric multiples (2:4:8:16, . . .) (15-20). These relationships, which have been proven repeatedly, indicate a constancy in the amounts of DNA per nucleus corresponding with a constancy of chromosome number, and it is generally held that the amount of DNA per chromosome set is approximately a constant. Synthesis of DNA resulting in doubling of the original amount normally occurs in the interphase preceding the next mitotic division (13, 14, 16, 20-25). If the DNA contents of interphase nuclei in a proliferating tissue are determined, a certain number will have DNA values intermediate between the clearly defined 2C' and 4C' means; these represent nuclei which are in the course of synthesizing DNA in preparation for division.

DNA in the cell exists in the form of a nucleoprotein, where it is linked both with histone and "residual protein" (*v.i.*) (4, 25, 26-29). It makes up from about 15 to 25 per cent of nuclei isolated in non-aqueous media, in most species (3, 8, 28). The DNA molecule itself is now commonly pictured as a polynucleotide bihelix composed of a deoxypentose-phosphate chain whose nitrogenous bases, attached in glycosidic bonds are directed inward toward the axis of the spiral, where they are paired, through hydrogen bonds, with the complementary bases of another interlocking polynucleotide strand (30). A chain of basic protein is pictured as wrapped around the backbone of the DNA spiral (31). A possible mechanism for the self-replication of this structure has been proposed by Bloch (32), in our laboratory.

The characteristic native absorption of ultraviolet light by nucleic acids, with a maximum at about 2600Å, is due to their purine and pyrimidine bases.

The dissociated phosphoryl groups of DNA are responsible for its basophilia resulting from the formation of dye nucleate salt-like complexes. The cationic dye methyl green has been thought to have a selective affinity, under certain conditions, for polymerized DNA (33, 34) to which it can bind stoichiometrically (35). It has accordingly been proposed and used for microspectrophotometric quantitation of relative amounts of DNA in single nuclei (36). The fact that DNA loses its stainability with methyl green after depolymerization (34) or after certain treatments has also been invoked in the past to explain impairment of methyl green staining in terms of depolymerization or changes of molecular con-

figuration (33, 37-41). It is now generally understood that in cells basic dye binding by DNA results from an equilibrium involving several factors (pH, ionic strength, type of dye, etc. (20, 42-45) chief among which is competitive interference by basic groups of associated proteins, and steric hindrances by protein (43, 46). Methyl green is relatively selective only when factors determining the dye nucleate equilibria are controllable. When other factors are accounted for, differences in methyl green binding may reflect alterations in amount or type of the proteins associated with DNA, a property which has been turned to advantage in studies of changes in the deoxyribonucleoprotein complex in various cell states (47).

The Feulgen reaction is specific for DNA and depends upon the combination of leucofuchsin in a colored complex with aldehyde groups which are exposed on the deoxypentose sugar after controlled hydrolysis and release of purine bases (20, 43, 44, 48, 49). It is relatively unaffected by those changes in molecular configuration or association with protein to which methyl green binding is markedly sensitive. Measurement of amounts of DNA revealed by the Feulgen technique therefore afford a standard of reference against which other staining properties of DNA can be compared. Methyl green and Feulgen dye binding can be measured in sequence in the same nuclei, and a Feulgen-methyl green ratio determined. Under controlled conditions, this ratio is informative concerning DNA-protein relationships, and perhaps in exceptional circumstances, about the molecular state of the DNA.

2. Ribonucleic acid (RNA) is a regular constituent of chromosomes where it may constitute from 0.15 to 12 per cent of the total nucleic acid (8, 27, 28, 50, 51); it is the sole nucleic acid of nucleoli (plasmosomes) (27, 28, 52-54) in which its concentration probably does not exceed 5 per cent (54). The RNA in these locations can be demonstrated by means of basic dyes such as the thiazines and pylonine (50-52, 55), especially after use of deoxyribonuclease. Microspectrophotometry in the ultraviolet range, especially when conjoined with the use of specific nucleases, has been the principal means of semiquantitative estimation of nuclear RNA *in situ* (53, 56) although very considerable difficulties of interpretation are encountered with this method. Nuclear RNA, in striking contrast to the constancy of DNA, varies considerably in amount in the different cell types of an organism, and in different functional states (27, 28, 51, 56). While the origin and role of nuclear RNA have not been precisely defined, RNA appears to be especially associated with the heterochromatin of the resting nucleus and there are many evidences which suggest that it has a key role in endocellular protein synthesis (56).

3. Histones are strongly basic proteins peculiar to nuclei where they presumably are bound to DNA by salt-like linkages (4, 26-28) as histone deoxyribonucleates. The histones are thus integral components of chromatin. They are present in isolated chromatin threads in amount approximately equal to that of DNA (4, 28). They are metabolically more stable than the other nuclear proteins (57). There is some evidence that histones may be of specific composition and configuration in cells of the same type in any species. This has suggested to some that they regulate the activity of the genes and hence differentiation (58). By virtue of their high isoelectric point, basic proteins such as histones can be selectively and quantitatively demonstrated *in situ* by their binding of the anionic dye fast green at alkaline pH after removal of nucleic acids, according to the method of Alfert and Geschwind (59). A modification of the Feulgen procedure which insures retention of protein during hydrolysis permits revelation successively of DNA then histone in the same body (25). In this way it can be seen that in normal nuclei histones are invariably localized only wherever DNA is found, and have precisely the same particulate distribution. Bloch and Godman (25) have shown cytochemically that the syntheses of DNA and histone proceed simultaneously, resulting in doubling of both these substances prior to cell division, and have suggested that the synthetic processes of DNA and histone are inextricably linked. The alkaline fast green binding, since it depends primarily on salt-like union of an anionic dye to the positively charged amino and guanidyl groups of histones, is subject to competitive interference effects from anionic ions and groups, as well as steric or other masking, analogous to that affecting basic dye binding by nucleic acid. A major fraction of most histones owes its basic-

ity to a high content of arginine residues. These residues may be revealed *in situ* by a modified Sakaguchi technique, a procedure relatively untroubled by competing groups or macromolecular screening. This serves as a useful check on the alkaline fast green method for histone.

4. Nonhistone proteins of the nucleus. The chief constituent of the chromosomal residue after extraction of nucleohistone is a "higher" tryptophane-containing protein referred to by Mirsky and Ris (4, 28) as "residual protein". Both residual protein and DNA, which are firmly linked, are said to be essential for the morphological integrity of chromosomes (4, but see 27). The residual protein varies widely from tissue to tissue (28) and also in different phases of the cell cycle (47). Tracer experiments show that the "residual protein" has an incorporation rate of N^{15} in labelled glycine comparable to that of cytoplasmic proteins and higher than that of histones (28, 57). The residual protein is also an inhibitor of the basic staining of DNA (4, 47).

In addition to "residual protein", the nucleus contains proteins soluble in saline, of which the chief fraction is a globulin. They may amount to nearly one-half of the dry weight of the nucleus. Because of their solubility in aqueous solutions, some of these proteins may presumably be lost from ordinary histochemical preparations. A lipoprotein is also present in nuclear material (28). However, little is known about any of these proteins at present. Quantitative cytochemical methods for protein groups can be applied to reveal total intranuclear protein. The quantitative binding of naphthol yellow S (flavianic acid) to the amino, guanido, and imidazole groups of lysine, arginine and histidine residues respectively has been validated for cytochemical use by Deitch (60), who also showed that it may be employed concurrently with the Feulgen reaction, permitting successive cytophotometric measurement of DNA and protein in the same nucleus. An improvement of the well known Millon test for tyrosine residues is also useful for the estimation of total protein in nuclei (61).

CYTOPHOTOMETRIC METHODS FOR QUANTITATIVE ANALYSIS

Microspectrophotometric analysis is the only technical modality permitting a quantitative estimation of the relative, and sometimes absolute, amounts of absorbing substance in any individual nucleus in a mixed population. It is required when only microscopic samples are available for determination. For chemical studies of pathologic cell states microspectrophotometry (cytophotometry) becomes indispensable especially when a given morbid appearance of particular cells is to be compared with their chemical constitution, at any stage in the development of a cellular lesion. The natural absorption of nucleic acids and proteins in the ultraviolet range (2600–2800 Å) makes possible microabsorption photometry as extensively practiced by the Stockholm school (56, 62). Their absorption curves and photographs have been subject largely to qualitative and semiquantitative interpretation. The technical difficulties and sources of error involved in work with ultraviolet light are considerable (20, 43, 56, 62–64). Cytophotometric analysis in the visible spectrum is regarded as more specific and more versatile, and capable of minimizing many of the difficulties inherent in ultraviolet cytophotometry. In microspectrophotometry with visible light the optical density (absorption; color intensity) of microscopic objects of measurable geometrical dimensions is determined after chemically specific color developing reactions have been performed. The range of substances measurable in this way is limited only by the number of chromogenic reactions which have quantitative chemical validity, i.e. which obey the Beer-Lambert laws, and by the size and homogeneity of the objects to be studied. Cytophotometry in the visible light range has been employed in many studies and is an accepted method of quantitative cytology. In theory, it consists of a source of monochromatic light and a microscope surmounted by a spectrophotometer. Although relatively simple in principle, the physical systems, technicalities of instrumentation, and possible sources of error must be understood in order to apply the method usefully; these have been the subject of a number of critical reviews (19, 20, 43, 63–66). Measurements of the DNA per

cell in a "diploid" population of fixed nuclei, using ordinary instruments may vary by no more than 5-15 per cent. Among the most important of the errors to which cytophotometric measurement is subject is that resulting from inhomogeneous dispersal of chromophore packets (distributional error). This can sometimes be reduced in normal nuclei by proper techniques of fixation or preparation. In some of the pathological alterations studied, as in those nuclei containing viral inclusion bodies the objects to be measured are quite inhomogeneous and recourse must be had to the two wavelength absorption curve analysis method of Patau (67) and Ornstein (68) for correcting for distributional error. On the other hand, pathological alteration of nuclei such as occur in pyknosis and in lupus tends to render their contents more homogeneous, and tend to nullify the distributional error.

In the studies reported in the present communication, cytophotometric measurements were made with a microspectrophotometer incorporating Moses' (65) and Pollister's (66) modifications, using a battery-buffered tungsten light source from which the desired wavelengths were isolated with a monochromator. Results of the measurements are expressed in terms of arbitrary rather than absolute units.

DISTURBANCES AFFECTING PRIMARILY THE NUCLEIC ACID COMPOSITION OF NUCLEI

Normally the stable state of DNA in cells is changed only when chromatin duplication, such as that preceding cell division, or in endomitotic cycles leading to polyploidy takes place. In these cases, DNA and histone synthesis occur simultaneously during interphase, and total nuclear protein together with nuclear volume increase somewhat more slowly [autosynthetic growth (47)]. Apart from such reproductive growth, the amounts of DNA per nucleus are remarkably stable throughout marked physiological changes which may be associated with great increases of nuclear volume, and greatly altered cell activity (69-71).

In Tumor Growth

It has seemed reasonable to suppose that the DNA contents of tumor cells would show a pattern different from those of normal cells because of their higher proliferative rate, their aberrant divisions, chromosome counts and structures, and those alterations of volume, nucleolar size and chromaticity which have long arrested the attention of pathologists. Cytophotometric studies on a variety of tumor types indicate that the tumors have increased mean quantities of DNA (72, 73) and the relative amount of DNA per nucleus are generally distributed into classes in geometric (1:2:4) progression (74, 75). There is a greater variability about the mean, however, than in homologous normal tissues. The results are explained by the occurrence of nuclei with intermediate DNA values, and by the presence of higher tetraploid and polyploid DNA classes which reflect increased premitotic duplication, polyploidy, and aneuploidy, but not an actual disturbance of DNA synthesis.

Improved techniques making possible the accurate measurement of DNA of individual cells in all mitotic stages as well as in interphase, have been applied to a study of two mouse ascites tumors (76, 77). The distributions show a wide spread of figures about 8C at metaphase, and a small scatter of figures about 4C at telophase, indicating that in this tumor, cells which depart from the 8C DNA value and which constitute a large proportion of the sample, are not successful in multiplying. Such observations agree with the results of studies based on chromosome counts, and it has accordingly been postulated that tumor growth

is due mainly to the division of the stem cells (DNA content of 8C' in the example cited) which give rise both to new 8C' stem cells and the remaining aberrant cells [stem cell theory (78)].

In Viral Infection

More dramatic changes in the DNA accompany intranuclear viral infection. This is suggested by the presence of Feulgen staining inclusion bodies. Of particular interest are those viruses which aggregate into crystalline masses within the nuclei of parasitized human cells. Typical of this group are some strains of the adenoviruses (RI-APC'), which are the agents of a number of human disease syndromes. The intracellular appearances of these in cultured HeLa cells have been detailed by Morgan et al (79), who described the development of the viral particles in the nucleus, where crystal formation occurs. The histochemical and electron microscopic features of the intranuclear aggregates of adenovirus in HeLa cells infected with viral types 3, 4 or 7 were correlated in a study in which the same cells could be identified with both the electron and light microscopes (80). This entailed cutting adjacent thin ($0.05\ \mu$) and thick ($2-4\ \mu$) sections of osmium fixed methacrylate embedded cells and carefully mapping the sections in order to relocate the same cells under each microscope. Intranuclear crystalline aggregates which were seen with the electron microscope to be composed of ordered arrays of viral particles of about $60\ m\mu$ diameter, contained DNA as shown by the Feulgen reaction (Fig. 1). Because of the close packing of the particles in the crystals and the apparent absence of interstitial material, it is justifiable to consider that materials, such as DNA, identified in the aggregates are constituents of the viral bodies themselves. For this reason, nuclei containing crystalline inclusion bodies composed of virus can be studied cytochemically in terms of the relation of viral constituents (identified as Feulgen-staining inclusions) to host materials. In the type 3, 4 and 7 adenovirus infection an osmiophilic reticulum which did not itself contain nucleic acid first appeared in the nucleus; DNA-containing viral particles developed from and at the apparent expanse of this matrix. The nucleoprotein of the viral aggregates, which formed the intranuclear inclusion bodies, had properties different from those of the host nucleoprotein, thus enabling a distinction to be made between them on the basis of the reduced affinity of the DNA in the virus for basic dyes. When infected cells fixed in buffered osmium tetroxide were submitted to the Feulgen reaction and counterstained with azure B under controlled conditions, the color of the latter dye, which was readily taken up in host chromatin, preponderated over the Feulgen color; in the viral aggregates on the other hand little azure was bound and the Feulgen color prevailed. Nuclear chromatin could thus be seen interweaving among the viral masses. This staining difference between viral and host DNA is thought to be due to the firmness and intimacy of the DNA protein bond in the viral particles, the protein effectively masking the phosphoryl groups of DNA. This protective effect of protein is probably also responsible for the increased resistance of viral DNA to extractive procedures (TCA; DNase) as well as for other observed dye-binding characteristics, a condition which per-

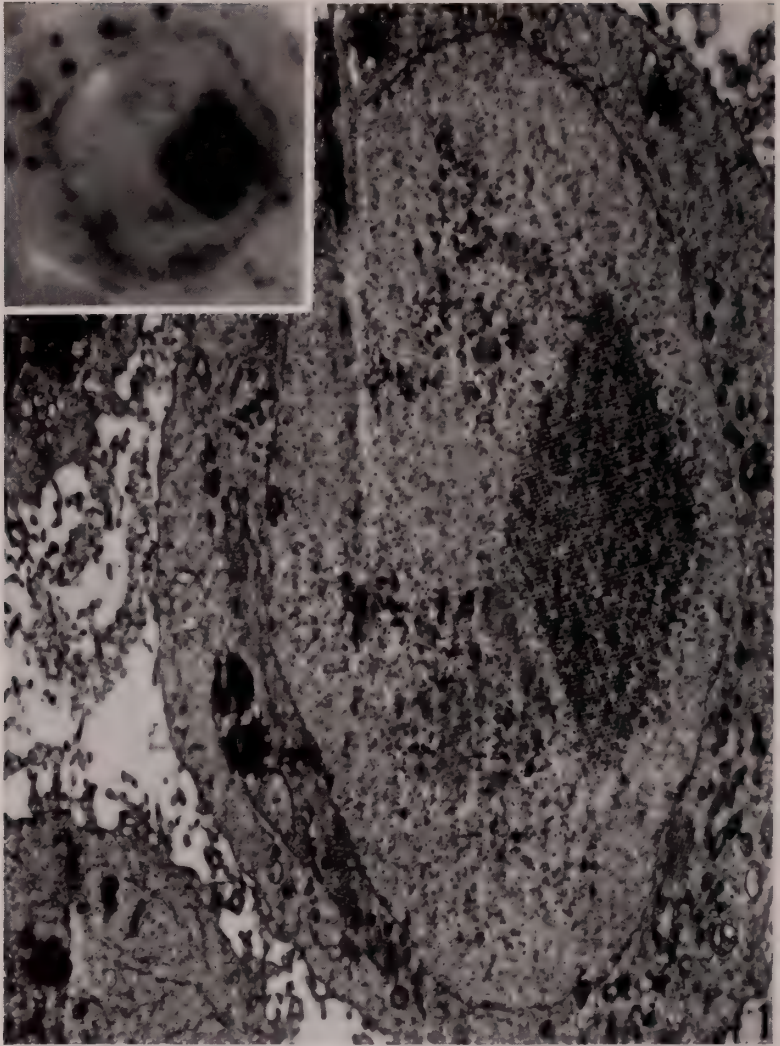


FIG. 1. Electron micrograph of a HeLa cell infected with type 7 adenovirus. In the nucleus is a well formed crystal composed of viral particles. Adjacent to it are two masses of osmophilic "matrix" material. $\times 6500$

The inset shows the same nucleus in the contiguous 3μ section used for histochemistry. The crystal is strongly Feulgen positive. The masses of dense osmophilic material are visible in the same relation to the crystal. $\times 1700$

mitted simultaneous revelation of the DNA of virus and histone of the host chromatin (81). Such morphological and histochemical observations pose many important problems of cytopathology concerning the relations between viral and cellular components, particularly at a chemical level. It will be important to gain some insight into the form, composition and activity of virus in the nucleus prior to the occurrence of distinct viral particles, the composition of the matrix material, the manner in which viral DNA is built up and the origin of the

materials from which it is made, i.e. to what degree is the substance of the host diverted to viral synthesis. While tentative answers to some of these questions have been obtained by biochemical methods in the case of the bacteriophages (82, 83) these can in no way be generalized. With the animal viruses, cytochemical methods, including also quantitative radioautography and immunochemical localization with fluorochrome antibody, closely correlated with light or electron microscopy, offer good prospects of yielding valuable information.

Quantitative cytochemical studies by Bloch and Godman (84) of another human virus similarly characterized by the formation of intranuclear crystalline aggregations have yielded interesting information on the synthesis of DNA in infected cells. Cells of the viral papilloma of human skin, which is the only tumor-like proliferation in man known to be of infective etiology, are familiar to pathologists for their intranuclear inclusions and intracytoplasmic masses (85-87). Bunting has demonstrated the presence of viral particles in the cells of the papillomata with the electron microscope (88). Pathological changes in the nuclei of infected cells have been found to occur in a definite progressive sequence from the lower stratum spinosum into the stratum corneum. In the earliest stage, a small acidophilic Feulgen-negative inclusion body is recognizable within cells situated one or two layers above the basal, but the nuclear morphology is otherwise undisturbed (Fig. 2). In subsequent stages the inclusion body and nucleus enlarge, and there occurs progressive disorganization of nuclear structure, as the chromatin clumps, becomes marginated, and subsequently diminishes (Figs. 3 and 4). The inclusion body of the later stages occupies most of the distended nuclear sac; it is basophilic and strongly stained by the Feulgen technique. The nuclear membrane may finally disappear, leaving a large naked homogeneous, Feulgen positive inclusion body within the cell remnant in the lower stratum corneum (Fig. 5). This body is believed to contain close packed crystalline arrays of virus (88). The relative content of Feulgen-staining DNA per cell was measured in nuclei of apparently normal epidermal cells and in nuclei at each stage in the evolution of the lesion in the infected cells. Determination of the DNA in the markedly inhomogeneous nuclei in some of the stages of infection was made possible by use of the two wavelength method of Patau (67) and Ornstein (68). In normal and hyperplastic epithelium frequency distribution plots of the relative amount of DNA per nucleus fall into the bimodal pattern with a layer 2C (diploid) and smaller 4C (tetraploid) class characteristic of reproductive growth in tissues (Fig. A). The infected cells were seen to have greatly increased DNA contents. Infection evidently entails prompt and rapid synthesis of DNA in the nucleus, for at the earliest recognizable cytopathological stages of infection, while the inclusion body was acidophilic and Feulgen negative, increased amounts of DNA from tetraploid up to approximately 16-ploid levels were measured. Levels of DNA were found not to increase appreciably throughout the subsequent development of the cellular lesion, nor was there generally any accumulation of nuclei into distinct classes as compared with intermediate amounts between them. In the earliest stages, however, there was evidence of a stepwise pattern of synthesis from 4C to 8C. At a relatively late stage in the infection, all of the

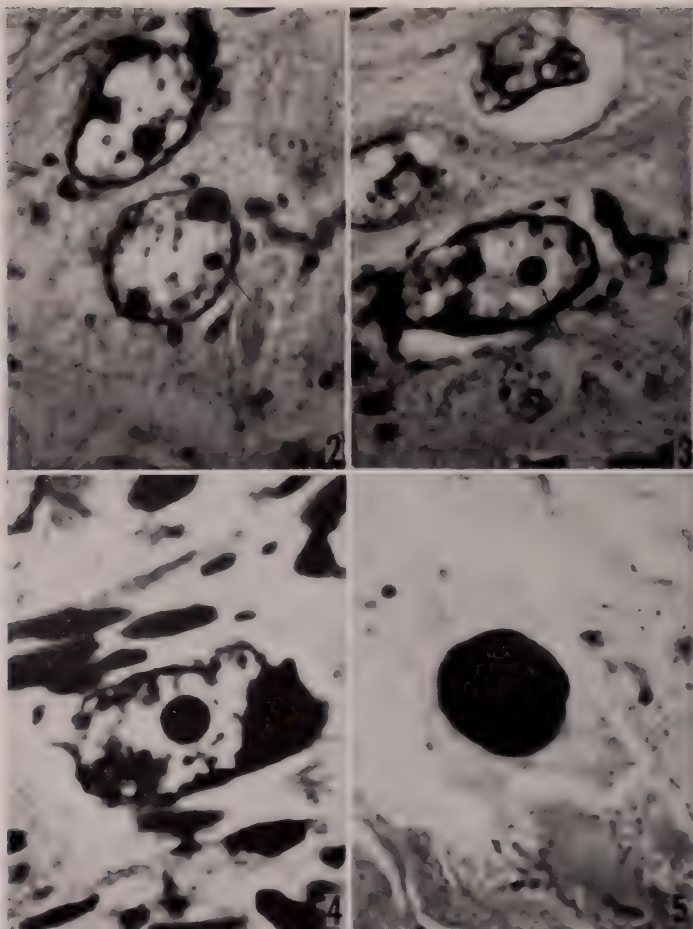


FIG. 2. Cell of the lower Malpighian stratum of a viral papilloma of human skin, showing the earliest recognizable stage of infection (A). The small eosinophilic inclusion body, indicated by the arrow, is surrounded by a narrow halo. $\times 1000$. Hematoxylin and eosin.

FIG. 3. The next morphological stage of infection (B), showing the larger inclusion body, clumping and margination of chromatin material, and some of the cytoplasmic masses characteristic of the lesion. $\times 1000$. Hematoxylin and eosin.

FIG. 4. A later cytopathologic stage (D) showing markedly enlarged inclusion body and further structural disorganization of nuclear components. $\times 1000$. Hematoxylin and eosin.

FIG. 5. Final stage (F), showing a large naked inclusion body within the cytoplasmic remnant. $\times 1000$. Hematoxylin and eosin.

cellular DNA apparently becomes "relocated" and reassembled in the mature inclusion body, without significant change in amount. From these studies it would appear that active synthesis of DNA in affected cells occurs only in fairly intact nuclei. The skin papilloma virus, like adenovirus, develops intranuclearly in connection with a nucleic acid free matrix, and aggregates into crystalline masses of viral particles containing DNA. The form in which the virus exists during the rapid, almost precipitous synthesis of DNA by the nucleus, and the composition of the matrix, are unknown. It seems likely that the increased DNA

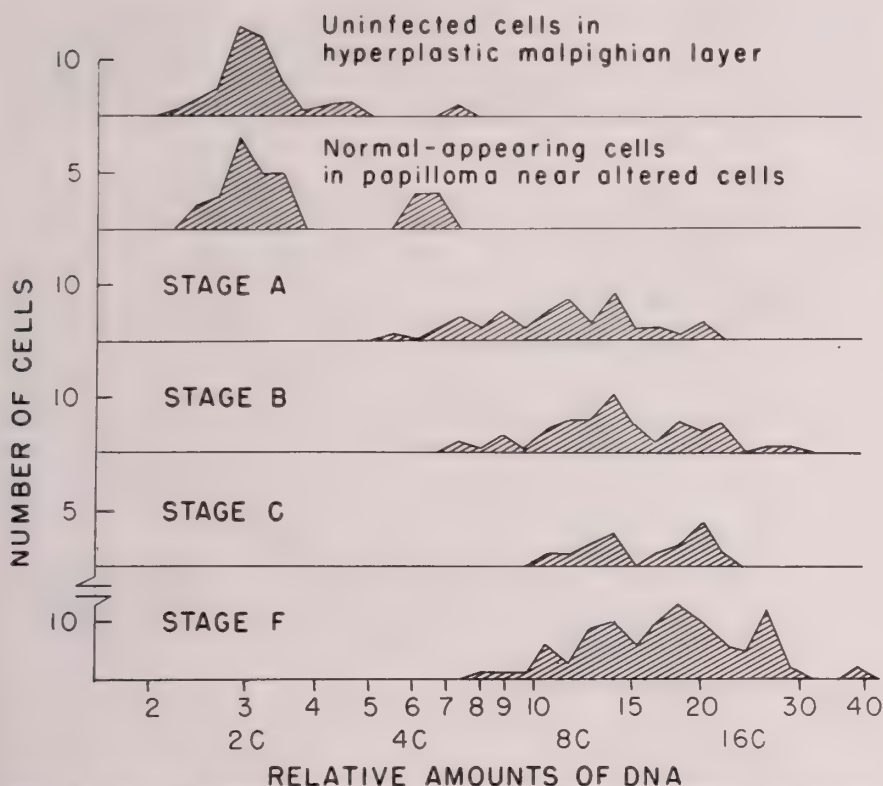


FIG. A. Frequency distribution curves of relative amounts of Feulgen-stained DNA in cell of some of the cytopathogenetic stages of the viral papilloma of human skin, and in adjacent normal appearing cells. In the earliest morphologically recognizable stages of infection (Stages A and B) characterised by the presence of relatively small eosinophilic inclusion bodies, a marked synthesis of DNA up to 8 times the diploid amount has already occurred. No significant increase in DNA occurs in later stages. Ordinates are linear; abscissa is logarithmic.

in the earlier stages is predominantly of host origin, and is replicated by a chromosomal mechanism, and that ultimately all of the nuclear DNA is broken down and reassembled as viral DNA, where it finally becomes localized in the viral aggregate (Fig. B). These data accord with the conception brought forward by several investigators (56, 82, 83, 86, 89) that certain viruses stimulate endocellular DNA synthesis and exploit or parasitize the DNA forming parts of the cell. That they simultaneously parasitize the protein forming mechanism of the cell as well is most probable, for intranuclear infection with these viruses apparently also entails large increases in protein content.

DISTURBANCES AFFECTING PRIMARILY THE PROTEIN COMPOSITION OF NUCLEI

In contrast to the DNA content, the total amount of protein in the nucleus varies greatly in the course of the mitotic cycle and in different physiological conditions. Bloch and Godman (47) have presented definite evidence of differ-

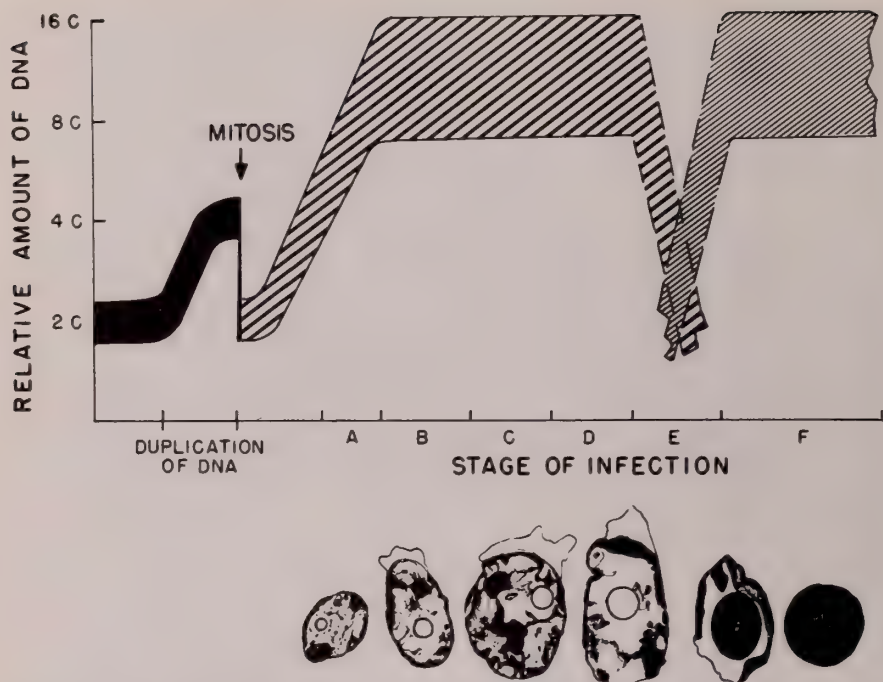


FIG. B. Diagram relating the DNA content per cell to the mitotic cycle and to the stages of infection with papilloma virus. The widely barred curve shows the DNA of the entire nucleus and its inclusions; the close hatched curve is the DNA of the mature inclusion. The appearances of the cells at each stage are sketched below the abscissa. "Relocation" of all DNA into the inclusion body occurs at E.

ences in the deoxyribonucleoprotein complex of interphase nuclei of proliferating (autosynthetic) and non-dividing i.e. presumably functioning (heterosynthetic) cells. In the autosynthetic interphase, DNA content, DNA basophilia with methyl green, and histone stainability increase concomitantly with nuclear size from 2C to double these values (4C) (normal reproductive growth). In heterosynthetic interphase, DNA content remains unchanged at the diploid (2C) level, but DNA basophilia with methyl green and histone acidophilia become markedly depressed, owing to the presence of a protein which becomes more closely associated with the nucleoprotein complex, and acts as a competitive inhibitor of staining. This protein, which may be the "residual chromosomal protein" (4, 28), becomes dissociated or lost from the nucleus during the autosynthetic interphase, since there is no impairment of dye binding at this stage by DNA or histone. An investigation along these lines of the nuclear contents during differentiation and in neoplasms should afford valuable insights into normal and atypical growth.

Striking changes in nuclear size and volume have been known to accompany cyclical physiological changes, especially in such hormonally regulated tissues as thyroid and endometrium. It has been shown, particularly in the researches of Alfert and his collaborators (69-71), that the amounts of DNA and histone, and

their stainability in such nuclei remains unaltered through marked variation of nuclear size and total protein content. The changing proteins in this case are therefore believed to be less closely combined in the nucleoprotein complex than those which appear in heterosynthetic cells.

Pyknosis

The similarity between mitosis and pyknosis with regard to loss of functional activity has been drawn by Leuchtenberger (40) and by Pollister (27), and it has been noted that in pyknosis changes in Feulgen and methyl green staining occur which parallel those taking place in the transition from hetero- to autotrophic interphase and in the chromosomal condensation of mitosis (47, 94). Cytophotometric examinations of the pyknosis in different materials (40, 90) are in agreement that this process of nuclear condensation involves at first a loss of protein. Alfert (90) has shown that this event is reflected in a marked increase of methyl green basophilia per unit Feulgen-DNA and a rise in histone acidophilia. This is due to unmasking of charged groups previously made unavailable by the associated nonhistone protein which becomes dissociated in pyknosis, leaving chiefly a condensed nucleohistone residue. Loss of some Feulgen-DNA occurs very probably as a later secondary event, through karyorrhexis (90) or karyolysis.

Lupus

A tendency opposite to that seen in pyknosis is manifested in the nucleoproteins during the nuclear alterations characteristic of systemic lupus erythematosus.

The transformation of the nuclei of leukocytes and other substrate cells to LE bodies by a factor travelling with the γ -globulins in the serum of patients with systemic lupus erythematosus has become a universally applied diagnostic procedure since its first description by Hargraves (91). The swelling, loss of chromatin structure, homogenization and alteration of tinctorial properties of the nuclear contents entailed in the LE conversion have since been repeatedly described. It is now clear that the hematoxylin bodies in the tissues are derived from such altered nuclei. The importance of this nuclear change in the pathogenesis of systemic lupus has been recognized through the investigations of Klemperer and his coworkers (39, 92, 93). The histochemical studies made in 1950 (39) seemed to point to an effect such as depolymerization, upon the DNA molecule itself. More recent studies by Godman and Deitch (94) undertaken with the collaboration of Dr. Klemperer, have attempted to define more precisely the nature and composition of the LE body and hematoxylin body.

The methyl green uptake in LE bodies was uniformly found to be depressed as compared with unaffected control nuclei (Table I). It has been pointed out in the foregoing discussion that selective methyl green binding by DNA is subject to a number of variable influences among which, under usual controlled conditions, competitive interference by protein associated with DNA is primary. The basic groups of the protein which compete with the cationic radicals of the basic dye for the phosphoryl groups of DNA can be destroyed by acetylation (46, 47, 60). When the methyl green binding by LE bodies and lymphocytes was com-

TABLE I

Mean amounts of methyl green and Feulgen dye bound in L.E. bodies derived from lymphocytes

Measurements of free (non-phagocytosed) L.E. bodies in L.E. preparations made with lymphocytes from a patient with chronic lymphatic leukemia. The data illustrate the effect of competing protein groups, which are destroyed by acetylation, upon the binding of methyl green by DNA in lymphocytes and L.E. bodies respectively. Acetylation results in similar Feulgen: postacetylated methyl green ratios for both, indicating that DNA is not depolymerized in L.E. bodies.

	Lymphocytes	L.E. Bodies
(No. measured).....	(20)	(20)
Methyl green.....	16.7 \pm 0.5	11.9 \pm 0.3
Me Gr after acet.....	17.8 \pm 0.8	23.1 \pm 0.6
Feulgen.....	19.9 \pm 0.4	21.3 \pm 0.5
Post-acet Me Gr		
Me Gr	1.06	1.94
Feulgen		
Me Gr	1.19	1.79
Feulgen		
Post-acet Me Gr	1.12	0.92

pared before and after acetylation, it was observed that while acetylation of competing protein groups effected a small (less than 10 percent) rise in dye binding in the lymphocytes, this treatment brought about an almost twofold increase in the methyl green binding capacity of the DNA of the LE bodies (Table I; Figs. 6-8). Thus, in the lupus body about half of the total stainable DNA was masked by protein. The Feulgen reaction, which, as noted, is less sensitive to changes in the state of DNA or its relation to protein affecting methyl green binding, is used as a standard of reference against which to compare changes in basic dye binding. In normal nuclei of lymphocytes and leukocytes the ratio of the amount of Feulgen revealed DNA to the amount of methyl green stained DNA is nearly constant and was found to be about 1.0; in the case of the LE body this ratio was higher, owing to depression of methyl green binding in them. After acetylation, the methyl green, Feulgen ratios in lymphocytes and LE bodies became similar (Table I), from which fact it was concluded that the DNA in LE bodies is not detectably depolymerised or altered in configuration. Moreover comparison of the amounts of Feulgen stained DNA showed that DNA is not lost in the course of the LE transformation (Table II). These data drew attention to the protein moiety of these altered nuclei. Inquiry into the location and amount of the histones by means of the alkaline fast green procedure (59, 25) elicited the information that this normal protein "partner" of DNA was either masked or absent from the LE bodies, and markedly reduced in the earliest stages of the transformation to the LE body (Table II; Figs. 9-10). The concomitant loss of Sakaguchi-staining arginine residues from such bodies suggests that histone is actually lost. In spite of this apparent loss of stainable histones, the total amount of protein in free unphagocytosed LE bodies demonstrable

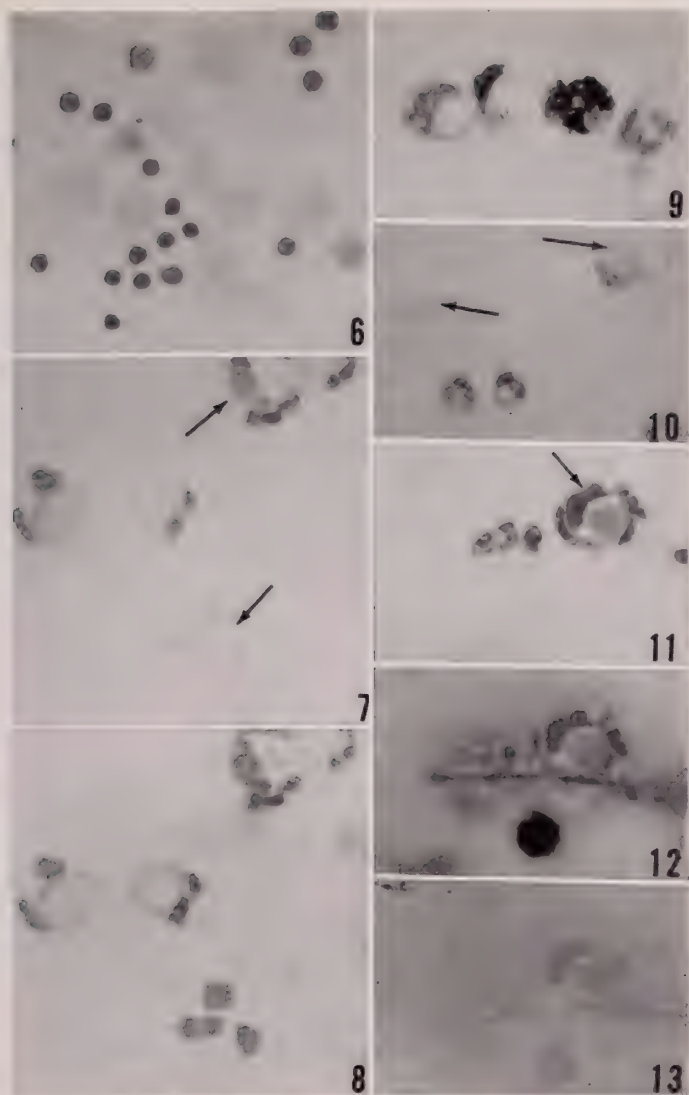


FIG. 6. Representative field of an L.E. preparation derived from lymphocytes of blood of lymphatic leukemia patient. The unchanged and pyknotic lymphocytes are interspersed among the large pale faintly stained lupus bodies. $\times 675$. Methyl green stain, red filter.

FIG. 7. Typical L.E. cells and free (non-phagocytosed) lupus bodies (arrow) derived from nuclei of polymorphonuclear leukocytes. $\times 675$. Methyl green stain, red filter.

FIG. 8. Same field as that of Fig. 7 after acetylation and restaining with methyl green. There is intensification of staining of the free lupus bodies and L.E. cell inclusions. $\times 675$. Methyl green stain, red filter.

FIG. 9. Typical L.E. cells, an eosinophil and a polymorphonuclear leukocyte stained to reveal basic protein of the histone type. $\times 675$. Alkaline fast-green, red filter.

FIG. 10. Polymorphonuclear leukocytes and some free lupus bodies (arrow) stained for basic protein of the histone type. The nuclei stain typically. The L.E. bodies are extremely faintly stained. $\times 475$. Alkaline fast-green method; red filter.

FIG. 11. An L.E. cell, a polymorphonuclear leukocyte and a red blood corpuscle. The nucleus of the original phagocyte (arrow) is itself beginning to undergo the lupus change. $\times 675$. Wright's stain, orange filter.

FIG. 12. Same field as that shown in Fig. 11 stained to reveal amino groups of dibasic amino acid residues in protein. The L.E. inclusion, the red corpuscle and the altered nucleus are heavily stained. $\times 675$. Naphthol yellow S, violet filter.

FIG. 13. Same field, stained to show tyrosine residues in protein. $\times 675$. Million reaction, blue-green filter.

TABLE II

Mean amounts of DNA and protein in L.E. bodies derived from lymphocytes

Measurements of free (non-phagocytosed) L.E. bodies in L.E. preparations derived from lymphocytes. The Feulgen data show that DNA is not lost in the course of the L.E. transformation. The marked increase of naphthol yellow S binding and Millon staining indicate the marked increase in total protein content in the formation of L.E. bodies. The decline and disappearance of alkaline fast green and Sauaguchi staining in L.E. bodies suggests a loss of histone.

	A Lymphocytes	B Early L. E. Bodies	C L. E. Bodies	Ratios	
				B A	C A
Feulgen.....	15.4 \pm 0.4	18.0 \pm 0.5	17.7 \pm 0.4	1.17	1.15
Naphthol yellow S.....	14.5 \pm 0.6	23.8 \pm 1.1	36.5 \pm 1.1	1.64	2.54
Alk. fast green.....	19.0 \pm 0.4	5.5 \pm 0.6	*	0.29	—
Sakaguchi.....	3.1 \pm 0.2	1.5 \pm 0.1	*	0.48	—
Millon.....	2.2 \pm 0.2	—	5.7 \pm 0.4	—	2.75

* Indicates below measurable limits.

with both naphthol yellow S and the Millon reaction (Figs. 11-13) was shown to be markedly increased in LE bodies (Table II). This was further confirmed in our laboratory by interferometric microscopy (95). This augmented protein apparently enters the nuclei of susceptible cells from extranuclear sources, probably from the serum. This protein, normally foreign to the nucleus, may be instrumental in disassociating the histones from the DNA and combining with the latter, where it would act to inhibit basic dye binding by DNA.

It thus appears more likely that the initial cellular transformation in lupus is centered on the proteins in the nucleus, and their bonding to DNA, and not upon the DNA molecule itself. In the tissues this new nucleoprotein material constituting the hematoxylin or LE body may be thought of as undergoing a further evolution, with aggregation, addition of proteins and other constituents and finally, gradual loss of DNA, eventuating in the extracellular proteinaceous deposits which Klemperer (93) and Gueft and Laufer (92) have equated with the fibrinoid material in systemic lupus erythematosus.

COMMENT

The division of these pathological events in nuclei into effects on nucleic acid and effects on protein is, of course, somewhat didactic. It should be clear that some changes, as in viral synthesis, or lupus, may eventually entail effects on both moieties.

The foregoing observations have been selected as exemplary of the way in which certain of the newer modalities of cytochemical investigation have served to explain and inform morbid morphological and tinctorial appearances long familiar to the pathologist. It is precisely because histochemical and cytochemical techniques must be conjoined with morphology that they are uniquely adapted to provide certain information obtainable in no other way, in spite of the limitations imposed by a relative paucity of applicable chemical methods.

Other avenues of investigation having similar aims are also beginning to provide chemical information concerning cell and tissue changes in disease. In describing "the history of material bodies" in terms of altered chemical composition, we are enabled to make more penetrating inquiries into the mechanism of their development and evolution, and so focus attention on the pathological process.

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RENAL HUMORAL (PRESSOR) VERSUS RENOPRIVAL (ANTIPRESSOR) HYPERTENSION

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The view that human hypertension may be of renal origin never has been seriously questioned, but it has been accepted unequivocally for only those cases in which there is a clear history of antecedent renal disease accompanied by renal excretory functional disturbance. The hypertension of diffuse glomerulonephritis and of bilateral congenital cystic disease of the kidneys is generally regarded as renal in origin. The objection usually offered to the idea that even the benign phase of so-called essential hypertension may be of renal origin is that, by definition, there is no significant disturbance of renal excretory function accompanying the elevated blood pressure. The virtually fixed resistance to the concept of the possible primary renal origin of essential hypertension is perhaps best epitomized by the opening statement of a recent editorial, by Wakerlin (1). "The pathogenesis of essential hypertension, which accounts for 95% of hypertension seen clinically, is still unknown despite extensive research in the past 25 years." It was shown (2), however, twenty-five years ago, that persistent hypertension produced experimentally in animals by moderate constriction of both main renal arteries, or by moderate constriction of the main artery of one kidney and ablation of the other kidney, resembles the benign phase of human essential hypertension hemodynamically in all respects, yet the experimental hypertension is not accompanied by significant impairment of renal excretory function, although it is obviously of renal origin. When, however, the constriction of both main renal arteries is excessive, or if one main renal artery is greatly constricted and the other kidney is excised, then the elevated blood pressure which develops is accompanied by disturbance of renal excretory function, uremia develops and, terminally, fibrinoid degeneration and necrosis of arterioles occur in many organs. This is a combination of clinical symptoms and pathologic changes characteristic of the malignant phase of human essential hypertension. The results of these experiments on animals indicate that human essential hypertension, in the benign and malignant phases of which obliterative renal arterial and arteriolar sclerosis of moderate or severe degree is practically always present, and in which the intrarenal hemodynamic disturbance is probably similar to that of the kidneys of animals with moderately or severely constricted arteries, also may be of renal origin. It is understood, of course, that any pathologic conditions of the kidneys other than arterial and arteriolar sclerosis, which produce similar impairment of renal hemodynamics, may also cause hypertension. In striking contrast to the opening statement of Wakerlin's (1) editorial, quoted above, Grollman (3) recently has epitomized the view of at least some of the investigators of experimental renal hypertension who believe in the renal origin of human essential

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hypertension, even though they may not agree about the mechanism of its development. "In view of the remarkable similarity between the hemodynamic, clinical and pathological features of hypertension as observed in the human and as reproduced in the experimental animal, the reluctance of some to accept the two as analogous seems unjustified and a hindrance to progress in the ultimate understanding of this disease." This expresses the view of those, like Grollman, who believe in the renoprival pathogenesis, as well as of those who believe in the renal humoral pathogenesis of experimental renal and of so-called essential human hypertension.

For the probable pathogenesis of experimental hypertension produced by constriction of the main renal arteries in animals, two main views have been advanced. Grollman's (3) view, to which the name *renoprival* was given by Kolff and Page (4), is based upon the hypothetical existence of a specific, non-excretory inactivating mechanism in normal kidneys which is capable of preventing elevation of blood pressure. The nature and mode of action of the hypothetical inactivating mechanism are not known, but the development of hypertension is considered the result of a decrease or impairment of incretory activity by reason of a reduction of renal tissue due to extirpation of disease. The other view (5) is that by reason of the change in intrarenal hemodynamics which results from constriction of the main renal arteries in animals, or from intrarenal or extrarenal (main renal artery) obliterative vascular disease of any kind in man, a substance of renal origin capable of inducing increased peripheral vascular resistance is released into the circulation and produces elevation of the blood pressure.

That a renal humoral pressor substance may be responsible for the development of experimental hypertension produced in animals by constriction of the main renal arteries, at least in the initial period (three or four months in the dog), is indicated by the results of many experiments which have been performed by different groups of investigators. Renin, an enzyme, extractable from normal animal and human kidneys, is present in much greater quantity in ischemic kidneys of hypertensive animals and in the nephrosclerotic kidneys of human hypertensives.* It is present in only minute amounts in systemic and renal venous blood of normal animals, and in the systemic blood of normal man, but it occurs in much larger amounts in the systemic blood, and especially in the renal venous blood, of animals with hypertension due to constriction of the main renal arteries, as well as in the systemic blood of human hypertensives, especially those who are in the malignant phase of hypertension. This has been shown indirectly by determinations of hypertensin in the blood (6-8). It is now well known that renin, not itself a vasoconstrictor substance, acting upon a substrate (hypertensinogen) in the plasma, induces the formation of hypertensin (angiotonin), a polypeptide, which is vasoconstrictor and therefore responsible for the vasopressor effect which renin exerts when it enters the blood stream. Although it has been believed generally that renin is effective experimentally only when it is injected directly into the circulation, yet Hessel (9) and we (with Dr. Erwin Haas, unpublished)

*Haas and Goldblatt, unpublished.

have found that it is also active when it is injected subcutaneously or intramuscularly; but by these routes it takes longer and a much larger quantity of renin (at least 100 units) to produce a 1 unit elevation (30 mm. Hg.) of the blood pressure. The pressor effect of such a large dose lasts longer, however, (at least 24 hours) than when a similar dose is injected intravenously, presumably because of the slow absorption and prolonged entrance of the enzyme from the subcutaneous or intramuscular site. Persistent elevation of blood pressure also can be produced by the continuous intravenous injection of renin or hypertensin. There is no tachyphylaxis to either of these substances when they are injected continuously in the way in which they probably enter the circulation of hypertensive animals. Because an increased amount of renin has not been detected in the systemic blood of animals with longstanding experimental renal hypertension, it has been suggested that a neurogenic or some other mechanism takes over and is responsible for the continued elevation of the blood pressure. The actual proof that this is so is still lacking and the possibility that, at this time, the vaso-excitor material (VEM) of Shorr and collaborators (9), or some other mechanism, may determine an unusual sensitivity of the peripheral vascular bed to hypertensin cannot be entirely excluded.

The renoprival (antipressor) and the renal humoral (pressor) theories of the pathogenesis of hypertension are agreed that the kidneys play an important part in the elevation of the blood pressure, but they differ about the mechanism whereby the elevation is effected. According to the renoprival theory, the elevation of blood pressure which follows unilateral constriction of a main renal artery is also the direct result of a reduction of an 'incretory', metabolic, antipressor activity of the kidney. If the renoprival theory were tenable for this, then one certainly would have a right to expect the development of hypertension as a result of unilateral nephrectomy. But unilateral nephrectomy does not cause elevation of blood pressure, while constriction of the main artery of only one kidney does, even when the contralateral kidney is normal. The excision of a kidney certainly reduces the amount of renal substance, and consequently the 'incretory' antipressor activity, much more than moderate constriction of one main renal artery, which usually has little or no effect on the mass of renal tissue, yet hypertension develops as a result of only the latter procedure. This is completely in keeping with a renal humoral (pressor) but not with the renoprival (antipressor) theory.

The strongest argument against the renoprival theory is afforded by the prompt fall of blood pressure which occurs as the result of the ablation of the ischemic kidney in an animal hypertensive as a result of constriction of only one main renal artery, or of the diseased kidney in man with hypertension associated with an abnormality of only one kidney of a kind which probably produces an intrarenal hemodynamic disturbance similar to that which results from constriction of the main renal artery. The most common abnormality of this kind is unilateral, chronic pyelonephritis with the obliterative intrarenal endarterial fibrosis and elastosis which accompany this condition. It has now been shown in more than 100 human hypertensives with unilateral renal disease and hypertension

that the excision of the diseased kidney, provided the other kidney is and remains normal, results in the prompt return of the blood pressure to normal. The most recent compilation on this subject is that of Homer Smith (11) who has reported that, of the 575 patients with unilateral renal disease and hypertension treated by unilateral nephrectomy reported upon up to the end of 1956, 149, or 25%, had had normal blood pressure for not less than one year and some for more than 10 years at the time of this report. Those in whom the blood pressure had returned to normal, but had not yet been normal for one year, were arbitrarily excluded from the list of "cures", but he refers to them as "probable successes". If the blood pressure were to remain normal in these cases for at least a year, this would increase the percentage of cures. The fact that many cures and many failures probably have not yet been reported would change the absolute numbers in each category but might not change the percentage of cures. Unreported cured cases, for as long as 15 and 18 years, are known to the author. In the case of the "cured" patients it is fair to assume that the contralateral kidney was normal at the time of the nephrectomy, but, in the case of the failures, although it is impossible to know what the state of the other kidney was, yet there is at least a reasonable probability that it was not normal, and perhaps the seat of vascular disease, despite the results of clinical and laboratory examinations which may have indicated that they were normal. The renoprival theory concedes that disease of the kidney plays a part in the origin of the hypertension, but it asserts that the diseased kidney plays its part, even in the case of unilateral renal disease, by merely reducing the amount of normal renal tissue available for the 'incretory' antipressor activity. The return of the blood pressure to normal, however, as the result of removal of the diseased kidney, cannot possibly be explained on the basis of the renoprival theory. This is one of the great stumbling blocks to the acceptance of the validity of this theory of the pathogenesis of experimental renal or of essential hypertension.

Congenital, or acquired (arteriosclerotic), partial obliteration of the lumen of one or both main renal arteries, often near the site of origin from the aorta, has now been found, by intra-aortic injections of radio-opaque material, in both young and older hypertensives (12); and correction of these abnormalities by transplantation of the renal artery or by an arterial graft, with the restoration of adequate renal circulation, has also resulted in the return of the blood pressure to normal. It is of particular interest that the almost invariable preoperative diagnosis in all such cases of unilateral and bilateral renal disease has been essential hypertension. The results of the operation are completely in keeping with the renal humoral (pressor) theory of the origin of so-called essential human hypertension.

According to the renoprival theory of hypertension, it is logical to expect elevation of the blood pressure to occur, and to begin almost immediately, after bilateral nephrectomy, but this does not happen. An animal may survive bilateral nephrectomy for as long as ten days without ever developing any elevation of blood pressure, if it is given no special treatment and is permitted to eat and drink in normal fashion. If, however, the animal is treated by either peritoneal

lavage or by the artificial kidney, then the blood pressure does rise, eventually, but there is a lag of several days before the elevation begins, and rarely does the blood pressure become as high as it usually becomes as a result of constriction of both main renal arteries. The hypertension of treated, bilaterally nephrectomized animals, which do not develop hypervolemia, is evidently the result of increased peripheral vascular resistance brought about by a disturbance of electrolyte and water balance (13), or in some other way still unknown. It is conceded that it cannot be the result of the entrance of renin into the circulation, because there are no kidneys and there is no other source of renin in the body. Since there is always some degree of azotemia in bilaterally nephrectomized animals, no matter how much they are subjected to peritoneal lavage or treatment with the artificial kidney, the elevated blood pressure which develops cannot be compared with the benign phase of experimental renal or of human essential hypertension. Because azotemia accompanies the hypertension, and because fibrinoid degeneration and necrosis of arterioles (often referred to erroneously as accelerated arteriosclerosis) have been observed at autopsy, in some bilaterally nephrectomized dogs (14), this hypertension, at most, resembles the malignant and not the benign phase of human essential or experimental renal hypertension.

An excellent example of the inadequacy of the renoprival theory was afforded recently by the successful transplantation of a normal kidney from one man with normal blood pressure to his hypertensive, identical twin brother. A report by Merrill et al. (15) made it clear that, after the transplantation, the hypertension persisted until the patient's own kidneys were removed, and then, with only one normal kidney remaining, the blood pressure soon fell to normal and has remained normal for many months. This effect is inconsistent with the renoprival idea because, logically, according to this theory, any reduction in the amount of normal renal tissue should have had the effect of raising the blood pressure still more; therefore, the diseased kidneys should have been retained to provide more renal tissue to help bring the blood pressure down. Excision of the diseased kidneys was logical only on the basis of a renal humoral (pressor) mechanism and the assumption that their presence resulted in the entrance into the blood stream of some substance which, directly or indirectly, was causing the elevation of the blood pressure. The fall of the blood pressure to normal as a result of the ablation of the two diseased kidneys, in this case, is completely in keeping with a renal humoral (pressor) mechanism as the basis of the hypertension.

What Grollman (16) offers as "the most direct evidence for the incretory role of the kidney in the pathogenesis of hypertension, namely, the depressor effect of extracts (of kidney) administered orally to rats", has not been confirmed in this or any other species.

SUMMARY AND CONCLUSIONS

A review of the salient features of, and difference between, renal humoral (pressor) and renoprival (antipressor) experimental hypertension indicates that these two hypertensive states involve different physiological mechanisms. The recent reports (11, 17) of many cures by unilateral nephrectomy, in cases of

human essential hypertension associated with unilateral renal disease, can be explained easily on the basis of the renal humoral (pressor) but not of the renoprival (antipressor) pathogenesis of the elevated blood pressure.

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HYPOPLASIA OF THE LUNGS

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Several types of congenital abnormalities are known to be associated with hypoplasia of the lungs in a high proportion of instances. In some of these, in which the infant is not viable because of the underlying abnormality, the peculiar condition of the lungs may contribute to early death. In other instances in which survival is possible, the properties of hypoplastic lungs should be reckoned with in order to prevent serious pulmonary complications. With these considerations in mind, all cases of hypoplasia of the lungs, and all instances of abnormalities which are known to be associated with that condition, were reviewed in material including approximately two thousand autopsies on newborn and stillborn infants.

OCCURRENCE

The abnormalities in which hypoplasia of the lungs is known to occur, include several types in which the space to be occupied by the developing lungs is markedly reduced, such as by diaphragmatic hernias, hydrops of the fetus with distension of the abdomen and pleural effusion, anencephaly with myeloschisis and deformity of the thoracic cage, achondroplasia and osteogenesis imperfecta of severe degrees affecting the ribs, and a variety of severe and uncharacteristic malformations which affect the chest in a more or less obvious manner. The explanation of the association with absence, hypoplasia or severe cystic malformation of the kidneys is not clear. Potter (1) has suggested that pressure of very large cystic kidneys may elevate the diaphragm and thus reduce the capacity of the pleural cavities. Actually, there is no correlation between the size of the kidneys and the degree of pulmonary hypoplasia, and the explanation of the association of these two conditions remains unknown.

Hypoplastic lungs were investigated with regard to their occurrence, structure, and behaviour on experimental expansion. The occurrence is shown in Table I. The material was limited to infants up to two days of age; it is almost certain that all infants with severe hypoplasia succumb within that time, with the possible exception of those with successfully repaired diaphragmatic hernias. In those surviving longer, mostly mild cases, the lungs would probably overexpand much like the remaining lobe of a lung after lobectomy, and thus become unrecognizable. All cases of diaphragmatic hernia which were not operated upon, and all instances of fatal achondroplasia, osteogenesis imperfecta, anencephaly and hydrops of the fetus are listed in Table I. Of malformations of the kidneys, those are included in which the amount of normal renal parenchyma was severely reduced. In the remaining two groups, namely, "miscellaneous malformations" and "no associated abnormalities", only cases with hypoplastic lungs are listed

From the Margaret Hague Maternity Hospital, Jersey City, N. J.

TABLE I
Incidence of hypoplasia of lungs, and of rupture of hypoplastic lungs

	All Cases	Hypoplastic Lungs				
		Number	Per cent of total	Live born	Ruptured	
					Number	Per cent of live born
Diaphragmatic Hernia.....	24	23	96	18	2	11
Skeletal Abnormalities.....	13	11	85	10	1	10
Hydrops.....	35	15	42	8	2	25
Kidney Malformation.....	31	22	72	14	9	64
Anencephaly.....	28	15	54	4	0	0
Miscellaneous Malformations....		10		4	1	25
No other abnormality.....		1		1	0	0
Total.....		97		59	15	25

and no rate of occurrence could be determined. It is apparent that the most constant association exists in cases of diaphragmatic hernia; these had dislocation of large parts of the abdominal viscera into the chest, almost filling one pleural cavity and affecting the other one to a lesser extent by causing a shift of the mediastinum. Accordingly, the lung on the side of the hernia was extremely hypoplastic, and the other one less so. The lowest incidence of pulmonary abnormality was seen in cases of hydrops in which distension of the abdomen and pleural effusion varied from case to case, and in anencephaly where, as Potter (1) has stated, the lungs are affected only when the malformation of the nervous system and skeleton extends down to the thoracic region. The ten cases of "miscellaneous malformations" include the following: heart malformation with large heart; deformed epiglottis with incomplete obstruction of larynx; encephalocele, defect of chest wall and others; scoliosis and hydrothorax; abnormality of thoracic skeleton, arterial calcification and hydrothorax; short ribs, megalo-ureters but normal kidneys; iniencephaly (2 cases); defect of spine and other malformations; defect of pelvis and abdominal wall. The one case of hypoplastic lungs unassociated with other congenital abnormalities occurred in a 1012-gram premature infant with lungs weighing 9.5 grams.

STRUCTURE

Sections were available for microscopic examination in all instances. In addition, hypoplastic lungs of nine infants were artificially expanded in order to reveal their basic architecture and their ability to be aerated. In these experiments one lobe was tied in order to preserve it in an unaltered state; one lung was then expanded with fluid and the other one with air from cannulas inserted into the main bronchi. In some instances air and fluid were introduced simultaneously and under identical pressure, and the volume expansion was recorded. Introduc-

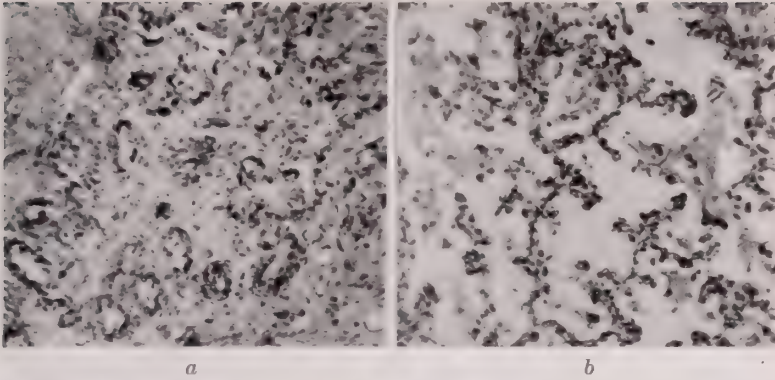


FIG. 1. Abnormal development of hypoplastic lungs. *a*, retarded development in a 1270-gram anencephalic; *b*, features more advanced than usually seen at this stage, in a 1440-gram infant with a large, malformed heart.

tion of fluid* expands lungs uniformly and with slight resistance; this unfolds the lung and reveals its architecture. Expansion with air, on the other hand, meets greater resistance and proceeds in less uniform patterns which vary characteristically with the degree of maturity (2).

Potter (1) has stated that hypoplastic lungs are likely to be retarded in the development of their air spaces; no other relevant data could be found in the literature. In examining sections of the present cases, it was striking to see most of the airless lung tissue collapsed, containing little or no fluid in the air spaces. In normal lungs, particularly in those of stillborns, partial expansion with fluid is common. The collapse was so complete in some instances that architecture and degree of maturity could not be made out. All lungs, including the completely collapsed ones, showed the well known relative preponderance of bronchi over parenchyma. Some of the severely hypoplastic lungs had small lobules separated from one another by wide septa of loose connective tissue. The degree of maturity was judged by the usual criteria, including thickness of the walls of the terminal air spaces, the presence of a cuboidal epithelium lining the spaces, the presence of alveoli proper, and the development of networks of capillaries bulging into the alveoli. Of those lungs which could be adequately examined, two-thirds were judged to be within normal limits in relation to body weight (allowance was made for overweight of hydropic infants, and slight underweight of anencephalics). In one-sixth of the cases development was found to be grossly retarded, and in an equal number significantly advanced. Retarded lungs were found only in infants with anencephaly, diaphragmatic hernia, and renal malformation; advanced lungs occurred in all categories. An example of retarded development with gland-like spaces lined by cuboidal epithelium and separated by wide septa, is shown in Figure 1a from a 1270-gram anencephalic. An advanced lung

* Since watery fluids escape from the airspaces and dissipate in the lung tissue, kerosene was used. Its interfacial tension against body fluids is a fraction of that of air and is negligible.

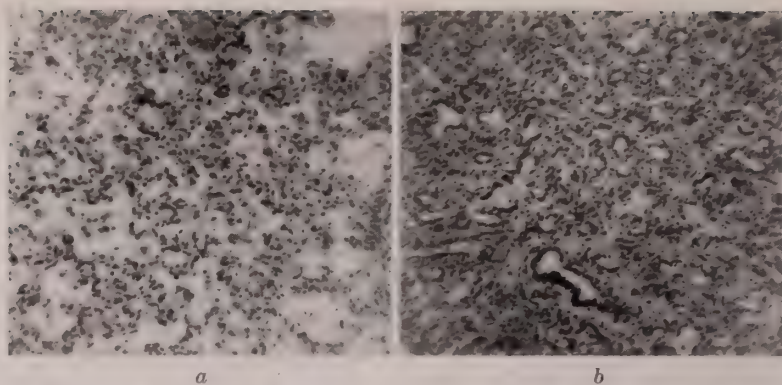


FIG. 2. Variation in degree of development in the lungs of one infant (2300-gram, diaphragmatic hernia). *a*, normally developed parenchyma; *b*, retarded portion.

with thin alveolar septa resembling the mature state, from a 1440-gram infant with malformed heart, is seen in Figure 1*b*. In a few instances variations between portions of the lungs were encountered, without relation to the degree of encroachment upon the lung. In the example shown in Figure 2, a 2300-gram infant with diaphragmatic hernia, the larger lung was retarded and the smaller one normal.

Experimental expansion of lungs is particularly desirable in the study of hypoplasia. The above mentioned tendency to complete collapse makes many hypoplastic lungs difficult to examine as they are found at autopsy. In addition, expansion with fluid in particular is helpful in studying those lungs which appear retarded or advanced as compared with specimens from normal infants of the same body size. These experiments might also bear on the tendency of hypoplastic lungs to rupture. The results of artificial expansion may be seen in Figure 3. The lungs of this 950-gram anencephalic were almost collapsed, with only slight and spotty expansion by fluid (Fig. 3*a*). Only the relative preponderance of bronchi can be seen in this state. Expansion with fluid (Fig. 3*b*) reveals thin-walled air spaces, as usually found only in much larger infants. Some of these thin septa project with free ends into lumina, thus resembling alveolar septa extending to the alveolar ducts in mature newborns. However, the number of alveoli thus formed is smaller than normally at term. Similarly, vascularization of alveolar walls is more extensive than is usual at this stage, but not quite comparable to the full-term infant. Expansion by air (Fig. 3*c*) is, as usual, less uniform than that by fluid, but the aerated spaces are expanded to a greater extent. Again, it is seen that the air spaces have thinner walls than in normal infants of comparable size, but are less extensively branched than at term. As far as can be judged by the small number of artificially expanded hypoplastic lungs, and other specimens which are naturally expanded, this characterizes the lungs referred to above as advanced in development. It is possible that the sequence of developmental stages of hypoplastic lungs differs somewhat from the normal course. In agreement with this is the observation that the characteristic atelectasis of prematures (2) with expanded bronchioles and collapsed al-

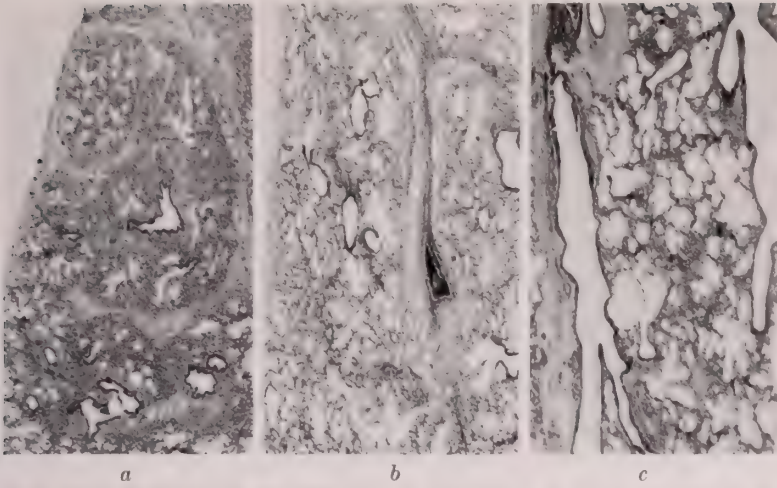


FIG. 3. Sections of the lungs of a 950-gram anencephalic. *a*, state at autopsy; *b*, another lobe, artificially expanded with fluid; *c*, another lobe, artificially expanded with air. All three photographs taken with the same magnification.

veoli, is rarely seen in hypoplastic lungs. However, this pattern appears only after air breathing or artificial expansion, and the number of relevant cases may not be sufficiently large to allow a definite statement on this point.

It has been supposed that respiratory movements in utero cause a tidal flow of amniotic fluid (3). On the other hand, the normal occurrence of intrauterine movements of sufficient extent to cause effective flow, is far from proven and has been seriously questioned (4). It might be tempting to speculate on the possible role of the absence or reduction of such movements in the development of hypoplasia of the lungs. This might occur in some of the conditions associated with pulmonary abnormality. In other instances, such as infants with hypoplastic kidneys, deficient production of amniotic fluid might interfere with this "breathing" process. Our knowledge of the normal processes involved is so poor that the possible significance of their abnormalities cannot be evaluated at this time.

RUPTURE OF HYPOPLASTIC LUNGS

Table I gives the incidence of rupture of lungs as indicated at autopsy by interstitial emphysema, mediastinal emphysema or pneumothorax. The incidence of 25 per cent does not indicate the full extent to which hypoplastic lungs are liable to rupture, since many of the liveborn infants in this group, for instance those with hydrops or anencephaly, never made adequate respiratory efforts and were not resuscitated with positive pressure. The entire autopsy material from which the present cases were derived, contains only 61 instances of rupture of normally developed lungs in infants under two days of age; hypoplasia therefore accounts for 20 per cent of all instances of rupture during this period of life, as seen at autopsy.

It is not known which property predisposes hypoplastic lungs to rupture. The

reduced amount of pulmonary parenchyma may contribute to this either by close proximity of relatively large bronchi to the periphery of the lungs, or by the small volume of distensible tissue, as pointed out by Wilson (5). In connection with the latter possibility it is of interest that rupture occurs most frequently in the hypoplastic lungs of infants with renal abnormalities (Table I) in which the thorax is capable of considerable expansion, whereas it is less common in those instances in which the volume of the pleural cavities remains encroached upon even when respiration is attempted (e.g., diaphragmatic hernia).

All but two of the 15 instances of rupture occurred in infants with a body weight of more than 2000 grams. Six of the cases were found in infants whose lungs were judged to be retarded in development of their parenchyma, and none in lungs considered to be advanced (see above). This suggests a possible predilection for retarded lungs of large infants, which again points to a disparity in the distensibility of the lungs on the one hand, and the chest on the other hand. This, according to Wilson (5), puts those small areas of lung tissue which will expand, under increased stress and causes their rupture.

Experimental expansion with controlled pressure has only been undertaken in four instances. This limited material did not yield results which were different from those obtained with normal lungs. One lung ruptured when it was repeatedly expanded by air under 50 to 60 cm of water pressure for periods of up to 30 seconds. At this height and duration of pressure normal lungs also ruptured occasionally. On the other hand, a hypoplastic lung showing interstitial emphysema at autopsy, did not lose additional air from the air spaces after repeated inflation under pressures up to 40 cm for 30 seconds. The number of observations is too small to permit any conclusions.

Since most infants with hypoplastic lungs have other malformations of such severe degrees that they could not survive, rupture of the lungs in these cases is irrelevant from the point of view of possible salvage. Only in cases of diaphragmatic hernia, survival is possible after adequate surgical treatment; in these instances it might be well to remember the peculiar properties of hypoplastic lungs, and avoid vigorous artificial insufflation. Even these infants, however, often have dislocation of abdominal viscera so extensive, and defects of the diaphragm so large that they cannot be expected to survive. Infants with hydrops sufficiently severe to cause hypoplastic lungs, have so far not been saved. There remains therefore only a small group of infants with diaphragmatic hernia in which the prevention of rupture of hypoplastic lungs may be important for survival. On the other hand, one should be careful not to attribute interstitial emphysema or pneumothorax found at autopsy in infants with hypoplastic lungs, to improper resuscitation since methods safe and necessary for expanding normal lungs, may cause rupture of hypoplastic ones.

SUMMARY

Ninety-seven instances of hypoplastic lungs were found among approximately 2000 autopsies on infants, stillborn or dying within two days after birth. The abnormality is associated with a variety of congenital abnormalities limiting the

space in which the lungs develop, and with severe defects of the kidneys in which the association is unexplained. Only in one instance no associated anomalies were found.

Histologically, hypoplastic lungs show a relative preponderance of bronchi over the reduced amount of parenchyma. The latter is normally developed in the majority of cases; occasionally it is retarded, and in some instances it shows features more advanced than the body size would indicate.

Rupture of hypoplastic lungs occurred in 25 per cent of liveborn infants; its significance is discussed.

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AN AUTOMATIC RECORDING ULTRAVIOLET AND VISIBLE MICROSPECTROPHOTOMETER

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The need for more searching methods of investigating fine intracellular change is as old as the concept of the cell itself. Virchow indeed himself wrote "By calling attention to the cell, I desired to provoke investigators to inquire into the processes within the cell, to define that which happens within these smallest elementary organisms. And it was self-evident that an exact definition could be nothing else than to find the chemical and physical foundations upon which vital phenomena and the activity of the cell are based" (1). This admonition has had intermittent application during the intervening century but in recent years with the impetus of more meticulous and elaborate techniques, studies of pathological changes have steadily become more basic in approach. Among the newer methods currently receiving attention is microspectrophotometry, utilizing the media of both visible and ultraviolet light.

Caspersson (2) was the first to use the ultraviolet absorption of nucleic acids and proteins for cytochemistry in a remarkable series of investigations into cell metabolism. Despite its many applications, his cumbersome photoelectric apparatus had the disadvantage of not permitting the procurement of continuous spectra (3). Since 1936, there have been marked improvements in technique so that it has become possible to devise an automatic recording instrument that shortens the time needed to determine intracellular absorption spectra by a factor of at least hundreds of times. The pertinent improvements are: 1. Apochromatic reflecting-refracting objectives (4); 2. Better designed photomultiplier tubes and circuits (5, 6); 3. New illumination sources and methods (7).

Wyckoff (8) described a most elaborate double beam microspectrophotometer in 1951. This had been previously built by Sinsheimer. The instrument "chopped" the I_x and I_o beams at 90 and 900 cycles per minute respectively and had automatic limiting circuits to protect the alternating current amplifiers from overloading. Unfortunately the performance of this instrument with cells or tissues was not discussed. Pollister and Ornstein (9) constructed an ingenious double beam microspectrophotometer of excellent performance in the visible spectrum. Alignment of this mechanism is relatively tedious and the apparatus is quite expensive. It requires the use of complete double microscope systems as well as four reflecting surfaces in each channel that increase loss of ultraviolet energy. The need for multiple stable mirror mounts also contributes to complexity of construction. Moreover, no method for the successful automatic procurement of facsimile records of ultraviolet absorption spectra of elements of cell magnitude has been developed despite considerable advances in instrumentation in recent

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years. It is the aim of this paper to describe the construction of a new automatic microspectrophotometer and to indicate briefly a few examples of its application to obscure areas in pathology. The present instrument incorporates the advances noted above as well as certain new features that allow automatic recording in the ultraviolet and visible regions. The instrument provides distinct advantages with the combination of a double iris diaphragm in the image plane, a single microscope and a choice of amplifying methods. In its preliminary application to a series of problems to be indicated in summary, the instrument proved to be much simpler in operation than previous non-automatic point-to-point machines.

DESCRIPTION

The instrument was built in the period 1950-1953 utilizing the basic design of experimental recording spectrophotometers (10-13). It was devised to obtain two types of operation, each type with its own advantage. The alternating cur-

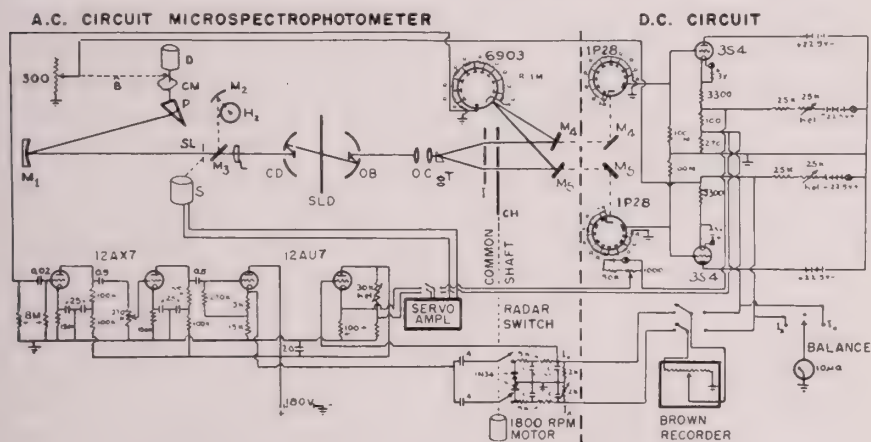


FIG. 1. Circuit of recording microspectrophotometer.

- P: Quartz prism.
 M₁: Collimator mirror.
 SL: Entrance and Exit slits.
 M₂: Off-axis paraboloid mirror.
 M₃, M₄, M₅: Plane Mirrors, First Surface.
 L: Simple quartz lens (Beckman).
 CD: Microscope condenser.
 SLD: Slide, 1 mm Quartz for Bausch and Lomb lens.
 OB: Microscope objective.
 OC: Microscope ocular.
 T: Side telescope of Leitz Micro-Ibso attachment.
 I: Double iris diaphragms for image plane, mounted on Leica Sliding focusing attachment.
 CH: Chopper for light beams. Each beam on its mirror $\frac{1}{4}$ cycle. (90°)
 B: Disc made of aluminum, counter weighted and mounted on ball bearings.
 CM: Fulcrum for lever of cam system.
 H₂: Aluminum cam on wavelength drive shaft.
 D: Hydrogen or Xenon arc.
 S: Wavelength drive motor $\frac{1}{2}$ RPM 6 watt Motor. (Gear reduction drive to prism.)
 S: Brown Servo Motor 57 RPM, driving slit thru string-and-plastic-pulley drive.

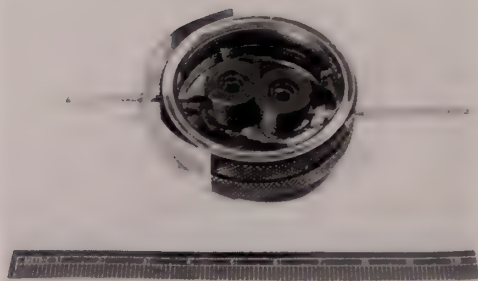


FIG. 2. Photograph of double iris mounting for Leitz sliding focusing attachment.

rent system is the first type, with the feature of absolute electrical stability. In this first arrangement, a single photomultiplier, light chopper, signal switch and single amplifier are utilized. The beams of light from the microscope are made to alternate in time in falling upon the same cathode area of a 6903 photomultiplier and are each on for one quarter of a cycle. Electrical rectifiers are used in the amplifier to eliminate the delicate phase adjustment of mechanical rectifiers. Areas down to 11 micra in diameter may have their absorption spectra determined from 2300 to 6500 Å. The second contrivance arranged was a double beam direct current instrument with two matched photocells and double amplifier systems. These modifications have permitted automatic computation of the ratio I_x/I_o (see list of abbreviations) by a "Brown" recorder and automatic control of slit width by a servo motor system in the A.C. and D.C. circuits, (Figure 1). The D.C. instrument had a much lower noise level and higher quantum efficiency than the A.C. instrument and permitted the study of one or two micron diameter areas down to 2300 Å, an improvement of roughly 36 times over the A.C. circuit, with however the disadvantage of long waiting for the attainment of electrical stability.

An important new feature of this machine is the optical separation of I_x and I_o in the last image plane of the single microscope. This is an improvement over the double microscope as used by Pollister and Ornstein (9) or the separate external optical paths for I_o as used by Sinsheimer, (8) Walker, (14) and Keohane (15). The device is shown in Figure 2. The arrangement allows symmetrical almost identical optical paths for the I_x and I_o beams. Two tiny iris diaphragms from Kodak 8 mm. f 3.5 movie lenses are mounted side by side for this purpose. They are adjusted to the same diameter when measuring spectra. Symmetrical portions of the monochromator slit illuminate each aperture. With the Bausch and Lomb N.A. 0.72 lens and a 10x ocular, I_x and I_o are 22 micra apart in the specimen. A small space is scratched in the tissue for the I_o beam. When I_x is in focus in the side telescope, I_o is also in focus, a unique feature of this system. Final image adjustment is made on a Leica sliding-focusing device arranged for right angle viewing. Quartz slides and cover slips are employed.

If the instrument is used as an A.C. machine the two beams are directed to the face of a 6903 flat cathode photomultiplier by small first surface mirrors, the only

mirrors used in the system outside of the monochromator and microscope (Figure 1). In the D.C. arrangement each beam goes to its own selected matched 1P28 photomultiplier with lightly sanded quartz envelope (13). Complete balance of spectral response in the 1P28's is provided by a simple aluminum scissor-cut cam operating a slide wire. This cam system is apparently new for microspectrophotometers. Other cam correction methods have been used in non-microscopic work (10). A warm-up period of several hours is needed before balancing the amplifiers and adjusting the cam. After this wait, results are readily reproduced, as in the superimposed spectra shown in Figure 6, representing the U.V. absorption of amyloid encountered in a case of cecal carcinoma. The monochromator is a Beckman DUV, the light source the Beckman hydrogen arc or the tungsten filament. A Hanovia xenon arc (Model 510 C) recently installed has improved performance immensely and has obviated the need for separate visible and ultraviolet light sources. The A.C. system is then adequate for most work. A Bäckstrom filter is needed in the U.V. in addition to the usual Corning 5693 filter to eliminate stray light (16). With the tungsten filament lamp a Kodak CC 30M filter is used to remove the 5500 Å peak with its extremely narrow slit (.03 mm. as a result of the slit servo action).

The A.C. instrument allows slit widths of .03 mm at 5500 Å (8.4Å effective band width) in studying a one micron diameter object. The D.C. instrument has a 2 mm slit width at 2300 Å (26Å effective band width) with a one micron object using a Beck water immersion solid quartz reflector lens N.A. 0.90 without ocular. "Noise" level (or statistical uncertainty) is kept to 1% for both wave lengths in these slit width specifications. Fixed slit operation in the A.C. instrument may be secured at attaching the slit servo motor to a rheostat in series with the photomultiplier voltage supply. Considerable improvement in performance would probably result by using a Perkin-Elmer prism monochromator (f 4.5) or a similar Bausch and Lomb grating instrument rather than the present f 12 monochromator. The Beck objective appears on the basis of preliminary tests to have the best light transmission of the high aperture apochromatic ultraviolet lenses available. This lens has an extremely limited working field however, and should probably be used only for objects less than 10 micra away from the field center (14). (The American Optical Co. 0.82 N.A. lens has not been tested.)

APPLICATION

A test absorption spectrum is shown in Figure 3. This is an ultra violet absorption spectrum of an epithelial nucleus in a normal renal tubule cut at 5 microns thickness. Formalin fixation was used as well as conventional paraffin embedding. The peak is roughly at 2600 Å as might be anticipated from earlier chemical analyses of deoxyribose nucleic acid content of nuclei. For purposes of quantitation it is necessary to calculate the volume, as, for instance, Kurnick's group (17) has done in their use of methyl green for stoichiometric estimation of deoxyribose nucleic acid content in cells.

Dyckman (18) was able to obtain absorption spectra of the renal inclusion bodies in cytomegalic inclusion disease with an earlier model of this instrument.

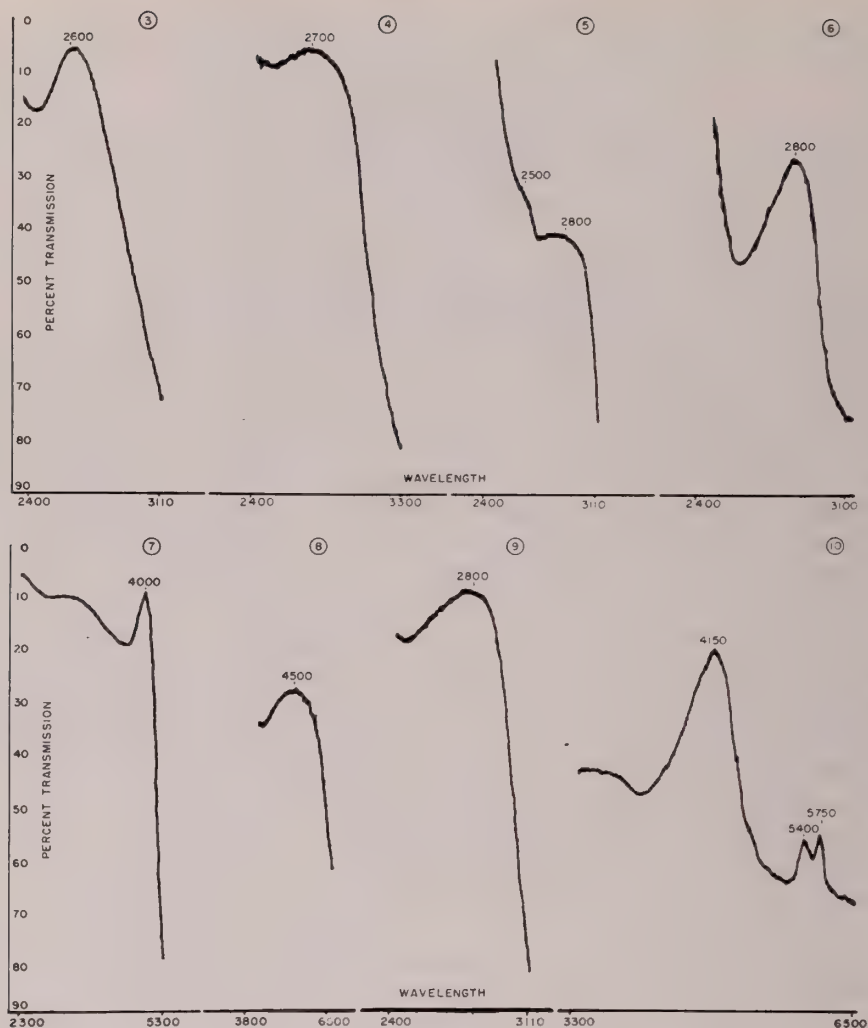


FIG. 3. Absorption spectrum of renal epithelial nucleus, 8 micron diameter.

FIG. 4. Absorption spectrum of cytomegalic inclusion, kidney, 3 micron diameter.

FIG. 5. Absorption spectrum of renal tuberculous amyloid, 6 micron diameter area.

FIG. 6. Absorption spectrum of renal glomerular amyloid, from a case of carcinoma of cecum, 8 micron diameter area.

FIG. 7. Absorption spectrum of Foá-Kurloff inclusion, 11 micron diameter.

FIG. 8. Absorption spectrum of carotene spot on slide, 11 micron diameter area.

FIG. 9. Absorption spectrum of "Hematoxylin Body," lupus lymph node, 5 micron diameter area.

FIG. 10. Absorption spectrum of living erythrocyte, 2 micron diameter area.

Subsequently these studies have been repeated with the present automatic recording instrument and Dyckman's findings of a broad absorption peak at about 2700 Å (Figure 4) have been confirmed. This absorption may be interpreted, along with staining reactions, as indicative of high concentration in the inclusion of DNA in combination with protein.

Studies are currently in progress for the purpose of determining variations in the absorption spectra among the various forms of amyloid. Significant differences in the U.V. absorption of these poorly understood deposits have been clearly distinguished, (19). The amyloid associated with tuberculosis in one case showed a 2500 Å shoulder and a relatively low 2800 Å peak as compared with primary and other secondary amyloids (Figure 5). The 2800 Å absorption seems characteristic of all amyloids tested and may be interpreted as indicating aromatic amino acids in protein (Figure 6). The Millon reaction was strongly positive utilizing Pollister and Mirsky's method (20). These findings agree with Hass' observations (21) that protein was associated with polysaccharides in amyloid. Wagner's chemical studies of amyloid deposits also support these findings (22).

The above work is presently being extended to other protein deposits with hyalin appearance. Because of its resemblance to the amyloids, the Kimmelstiel-Wilson glomerular nodule was investigated. In this condition, protein only was revealed, while the "wire loop" glomerular lesion of lupus indicated that in this condition, some DNA might also be present (19).

The hyalin inclusion bodies of guinea pig histiocytes induced by sex hormone activity, the Foá-Kurloff bodies, are also presently under investigation (23). These inclusions which measure up to 20 micra in diameter reveal a sharp high peak absorption at 4000 Å in addition to a lesser broader absorption at 2800 Å. A spectrum of this nature would apparently conclusively eliminate the possibility of any common sex hormone being present in the Foá-Kurloff cells since this absorption spectrum is unlike that of the hormones (24, 25). It is of incidental interest that a substance with this absorption spectrum should be yellow. This fact had not been noted previously but when the unstained inclusion was examined with white light of daylight quality, it was found to be yellow (Fig. 7.)

More recently this instrument has been utilized in a study directed toward the evaluation of the role of carotenes in coloring atheromata. Blankenhorn, Freiman and Knowles (26) have demonstrated that these fat soluble vegetable pigments may be used to trace cholesterol and other lipid metabolites. Preliminary trials with Blankenhorn have shown that an extremely small amount of carotene in a volume of 5 cubic micra on a slide yields a strikingly characteristic absorption spectrum (Figure 8), with a peak at 4500 Å (slit 0.12 mm). After a few days the peak shifts to longer wave lengths and multiple shoulders appear on the sides of the curves, a chemical characteristic of carotenes.

It is noteworthy that studies of "hematoxylin bodies" in systemic lupus supported Klempner's hypothesis (27, 19) that these masses contained large amount of desoxyribose nucleic acid. The Feulgen and Millon reactions were strongly positive, and the U.V. absorption had a broad peak at 2750 Å, (Figure 9) indicating the derivation of these odd structures from nuclear protein and nucleic acid. Recent studies show a characteristic ultraviolet absorption spectrum of the material in the "L.E. cell." This spectrum seems identical with that of the hematoxylin body, and thus further supports the opinion that the content of the "L.E. cell" and the "hematoxylin body" are both end stages of the same nuclear destruction that characterizes systemic lupus, (28).

DISCUSSION

Although these preliminary studies provide interesting and provocative data, caution in interpretation of results is as important in microspectrophotometry as in any new method of analysis. Even in the simpler spectrophotometry of solutions, incorrect results may stem from stray light, dark current shifts, impure solvents and shifting optics (29). In cell spectrophotometry, where more exquisite care is needed, maximal use must be made of standard existing information before conclusive interpretation is attempted. This is especially true in the ultra-violet spectrum. In the visible spectrum, non-specific absorption is relatively constant and there is close agreement with chemical data. In the case of intracellular hemoglobin (Figure 10) the spectrum represents an area of two micron diameter in an intact erythrocyte mounted in serum. This curve is almost identical with that derived from a hemoglobin solution. The uncertain state of U.V. microspectrophotometry is underlined by the controversy over findings which raged in an issue of "Transactions of the Faraday Society" (30). The orientation of molecules, the effect of non-specific absorption, the significance of fixed vs. living tissue, lamp stability, etc., seemed to precipitate violent difference of opinions.

Pollister and Ornstein (9) Walker (14), and Swift and Rasch (31) have discussed these matters in detail, and pointed out means of achieving rational results and valid interpretations in microspectrophotometry. Cell spectrophotometry must not be considered a useless bit of gadgetry as some have claimed, but there is no question that interpretation of results should be made carefully and cautiously. I am in complete agreement with Kavanagh's remarks in the "Conference on Microspectrophotometry of Cells" (32). He states "that workers in the biologic fields in general are accustomed from the nature of their material and their problems, to deal with and draw valid conclusions from data with a greater amount of variability or uncertainty than to which we in the so-called exact sciences of physics and chemistry are used." As Michaelis has aptly said "I wished to do more than stain a certain structure red which had previously been stained in blue," (33).

SUMMARY

1. An automatic recording microspectrophotometer for cytochemical investigation in the visible and ultraviolet regions is described. This makes possible the determination of absorption spectra of objects of size down to one micron.

2. The value of the instrument lies in its ease of application to many problems of cell research.

3. Although limitations exist, improvements are manifest in its application to certain biologic problems. These are discussed briefly.

LIST OF ABBREVIATIONS

A: Angstroms

N.A.: numerical aperture.

Ix: The light beam passing thru the object being studied on a slide.

- I_0 : The light beam passing thru a blank area of the slide.
A.C.: alternating current.
D.C.: direct current.
M.M.: millimeters
U.V.: ultraviolet
 f : optical aperture.
DNA: desoxyribose nucleic acid.

ACKNOWLEDGMENT

I should like to thank Dr. Arthur W. Pollister, of Columbia University, New York, for valuable advice, encouragement and material assistance in this field. Dr. Leonard Ornstein, of Columbia University and the Cell Research Laboratory of The Mount Sinai Hospital, New York, has been most helpful on many occasions over the past years.

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THE EXTRAVASATION AND PRECIPITATION OF URINE IN THE HILUS OF THE KIDNEYS

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It has been clearly shown in clinical pycelographic studies in man that with an increased pressure within the renal pelvis the dye contents may escape from the pelvis through the ruptured fornix. It may extravasate along the lymphatic channels or into the veins ("pyelovenous reflux" or "back flow"), or may spread diffusely into the tissues about the renal hilus and about the ureter (1, 2). From this it seems quite justifiable to assume that since substances artificially injected into the renal pelvis extravasate along these pathways, also ordinary urine may back flow in like manner under correspondingly similar conditions. Thus it was that Helmke (3) related certain peculiar precipitates in lymph vessels and veins ("lymph vessel and vein casts") to such extravasates of urine, and these he interpreted as urinary precipitates. One of us (H. H.) some years ago in two short articles concerned himself with the question of what happens with the extravasated urine in the peri-hilar tissues (4, 5), a situation analogous to the radio-opaque medium which infiltrates here but fails to escape along the blood or lymphatic channels. As reported, changes were found in the renal sinus tissues which were interpreted as urinary precipitates. The material collected since then (14 cases) and pertinent to this question has been examined by one of us (F. D. D.) and has been presented in a comprehensive report (6). In the course of these investigations some interesting general pathologic problems arose which we would like now to discuss.

The tissue changes produced by the extravasation of urine into the renal sinus are quite characteristic. *Grossly* one sees in the loose connective tissue and fat about the pelvis, especially in that between the calyces and renal parenchyma, typical peculiar glassy appearing gelatinous deposits. These usually are colored by associated hemorrhage, and vary from light brown to dark red brown (Fig. 1).

Histologically one finds in these regions a widespread separation of the constituent fat and connective tissues by finely granular to homogeneous masses of infiltrates in which isolated collagen fibers, individual fat and connective tissue cells are always engulfed (Fig. 2). At first glance of this histologic picture one might consider these homogeneous deposits to be most likely amyloid. However, the staining reactions for this substance are negative. These protein-rich precipitates are best demonstrated by the PAS stain, even after pre-treatment of the sections with diastase digestion. In this respect as well as in all other staining reactions these deposits react identically with the hyaline casts found in the lumens of the renal tubules.

From the Department of Pathology of the University of Bonn (Germany).

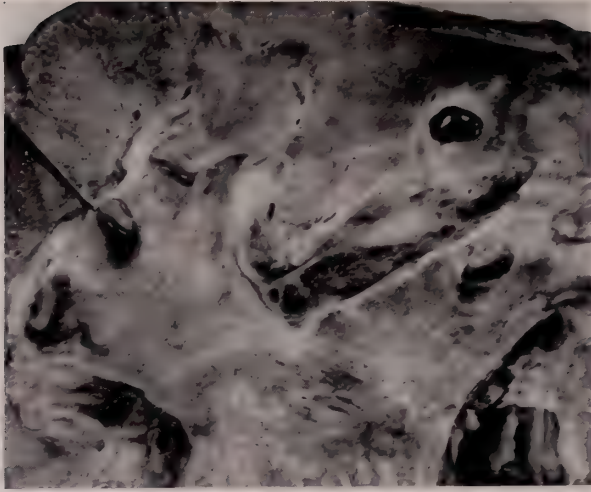


FIG. 1. 67 yr. old woman, with history of renal colic, renal lithiasis and nephrectomy (A8312/56). Sectioned kidney, the appearance and location of urinary extravasate typically seen in sinus fat about pelvis and calyces. The fat here is blood-tinged and gelatinous. Calyceal mucosa is granular and hemorrhagic, pelvis dilated.

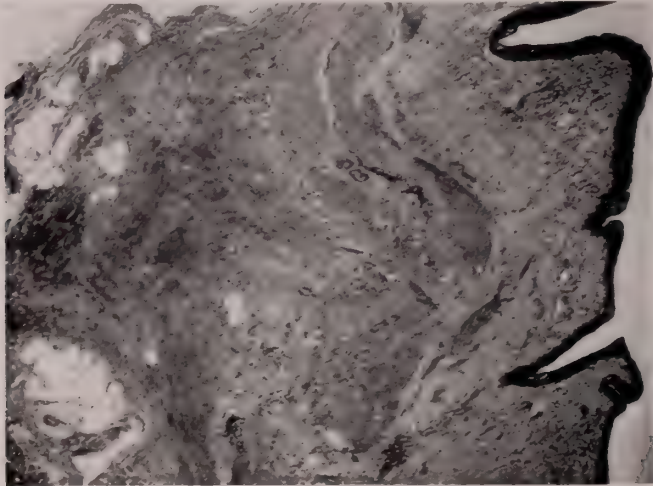


FIG. 2. Same case as Fig. 1. Urinary extravasate located in peri-pelvic tissues showing consolidation and the typical darkly positive staining with PAS. Magnification $\times 12$.

The *inflammatory reaction* induced by these homogeneous precipitates is typically low-grade, characterized in part by a scant infiltrate of lymphocytes about them. Neutrophils are rarely seen. At the margins one encounters macrophagic and fibroblastic activity. These cells ultimately grow into the deposits dividing them into fragments (Fig. 3). The macrophages may contain hemosiderin granules or fat droplets, this depending upon whether the homogeneous masses incorporate erythrocytes or fat cells. At first the fibroblasts produce reticulum

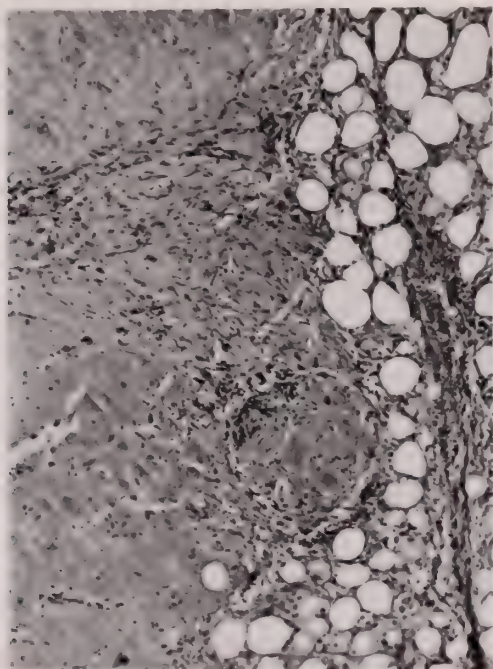


FIG. 3. Urinary extravasate located in renal sinus fat tissues. Fibroblastic ingrowth and chronic inflammatory cell infiltration at margin, but no vascular reaction. H. & E. stain. Magnification about $\times 54$.

fibers. Later collagen fibers are formed that eventually extend widely throughout the deposits (Fig. 4). Capillary proliferation is as good as lacking,—the process of resolution being primarily one of almost pure cellular repair; that is, it is a connective tissue organization of the deposits. On one occasion we observed within similar but larger precipitates the deposition of calcium salts. In another case we found new bone formation within the masses.

These deposits in the renal sinus tissues resemble in all respects those described by Helmke in the kidney parenchyma (3), and which he referred to as urinary precipitates. They stain similarly and are organized by the connective tissues in like manner (Fig. 5). There are other important reasons why these deposits are to be considered actually as a peculiar precipitate formed in part from the extravasated urine. In instances where the changes are of very recent nature one can often demonstrate the ruptured calyceal fornices, these being in direct continuity with the gelatinous masses in the peri-calyceal tissues. In those cases in which such rents in the fornices are not grossly evident, one can often by appropriate sections find a scar which extends to and involves the adjacent fornix. Finally, it should be pointed out that the urinary extravasates stain identically with the tubular casts (see above).

On the basis of these facts we would like to think of these peculiar gelatinous and homogeneous deposits in the renal sinus tissues as being the "trademark" of urinary extravasation through a ruptured fornix. We would like to designate

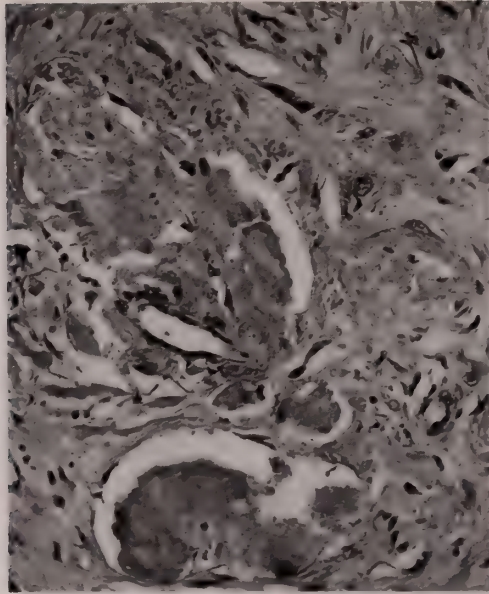


FIG. 4. 76 year old woman. Ureteral wall showing partially fragmented deposits in intramural (lymphatic channels?) spaces surrounded by lipophages and fibroblasts. H. & E. stain. Magnification $\times 160$. ACC. & AFIP. No. 5521398. (By courtesy of Dr. del Regato).

these unconditionally at the time being as "*urinary precipitates*", because we feel that the connotation carried by this term is in all probability correct. On the other hand certain important *questions remain yet unanswered*. Do these deposits represent a coagulation of plasma or a simple condensation or solidification of a protein rich fluid admixed with urine? Chemical analyses of these deposits are necessary, as well as attempts to produce identical masses either in the test tube or in the experimental animal by simulating those conditions occurring in the living human.

From the interpretation just presented it is clear that for the development of such urinary precipitates the *fornix rupture* plays a decisive role. However, the production of a forniceal rent depends apparently not only on an increased intrapelvic pressure, since we often fail to find forniceal ruptures and urinary extravasates exactly in those cases in which an especially high rise in the intrapelvic pressure has even lead to the atrophy of renal parenchyma—namely in hydronephrosis. A very essential factor in the production of a fornix rupture is as we know, the suddenness with which the intrapelvic pressure rises, as may occur in retrograde pyelography. However, it may also occur in excretory pyelography when pressure is applied to the renal pelvis or when colic develops (1, 2).

Such attacks of *colic* arising from an ureteral obstruction are therefore able to produce just that sudden elevation in pressure which may lead to fornix rupture and to the extravasation of urine. Corresponding to this we have in our material several cases of urinary precipitates without dilatation of the renal pelvis or calyces. On the other hand we have found no instances of urinary

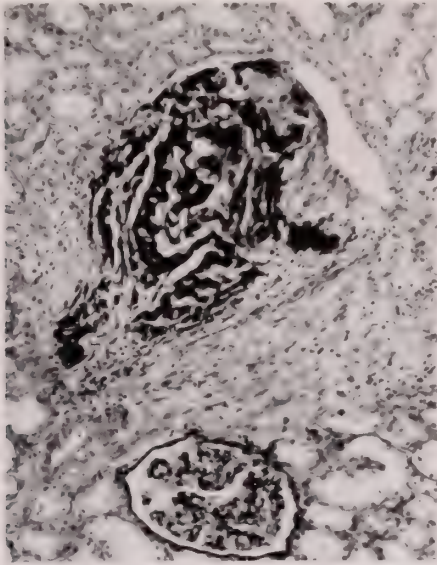


FIG. 5. 59 year old man with rectal carcinoma, and stenosis of left ureter by metastases. (S 755 56). Pronounced compression of renal cortical vein by intramural deposit of urinary extravasate. PAS stain. Magnification $\times 115$.

extravasation without an obstruction of the ureter. It is odd, that the fornix rupture and the resulting urinary extravasation as demonstrable roentgenologically and anatomically cause so few clinical symptoms.

Urinary extravasation and precipitation in the renal sinus is by no means just a pathologic curiosity. It is a finding which can also be of *clinical importance*. For as more and more collagen fibers are laid down within the precipitates, the resulting cicatrix may compress and narrow the calyx, the pelvis or ureter. It may at times simulate a tumor. The general recognition of these pathologic changes may provide some of the not now well understood stenoses of the ureters or renal pelvis with an explanation.

These urinary precipitates formed and removed by living tissues consist of a material formed by the body itself but which, however, acts like a foreign substance. There is an entire group of such *endogenously produced substances which act like foreign body irritants* in the tissues. We want to mention only two of these, because the reactions they induce show great similarities with those produced by the urinary precipitates: fibrin and epithelial mucin. Fibrin can also become overgrown by fibroblasts and eventually be replaced by connective tissue, an occurrence which we know as "organization" of thrombi and of fibrinous exudates. Analogous to this we may speak of an organization of urinary precipitates. When epithelial mucin, as the result of the destruction of glands or of excretory ducts, comes in contact with and infiltrates, so-to-speak, the connective tissues, a cellular reaction is induced (7 8). The organization of the mucin presents strong resemblances with that of the urinary extravasates: the elimination of it occurs primarily by the phagocytic activity of the proliferating macro-

phages, a reaction which we find in lower animals as the equivalent of "inflammation" (9),—a mobilization of phagocytes without exudation and blood vessel proliferation. In this regard it appears that the reaction of mammals to endogenous foreign body substances can exhibit common characteristics with those primitive inflammatory reactions seen in the lower animals (5).

SUMMARY

With a sudden rise in the intrapelvic pressure urine can extravasate through the ruptured fornices into the renal sinus tissues and lead to the formation of peculiar deposits that are readily recognized grossly. These become organized by the connective tissues in the same manner as foreign body substances. By cicatrix formation and contraction a stenosis may develop.

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ORIGIN OF POLYPLOID NUCLEI IN RAT LIVERS DURING REGENERATION FOLLOWING CARBON TETRACHLORIDE POISONING*

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The occurrence of polyploid nuclei in mammalian liver had been established by Jacobj's (1) study of nuclear volume classes in geometric series, by chromosome counts (2), and by photometric measurements of individual Feulgen-stained nuclei indicating a geometric progression of amounts of desoxyribonucleic acid per nucleus (3). A number of mechanisms have been postulated for the origin of the polyploid cells, three of which will be discussed here: (a) fusion of interphase nuclei (4), (b) fusion of nuclei at mitosis (5-7), and (c) endomitosis or chromosomal doubling without mitosis (8, 9). The first two processes require the presence of binucleate cells, probably arising by failure of cell division after nuclear division; the third does not.

It was found in the course of experiments on liver regeneration following carbon tetrachloride poisoning (10) that the proportion of nuclei in each of the three classes—diploid, tetraploid, and octoploid—was nearly constant in different individuals under specific conditions. The analysis of the frequencies of polyploid nuclei in these rat livers correlated with proportion of binucleate cells within each class has given strong support to the second hypothesis mentioned above, that the polyploids arise by fusion of metaphase figures at mitosis.

MATERIALS AND METHODS

Male white rats of the Wistar strain were injected with carbon tetrachloride as described by Hoffman *et al.* (10). Twenty-four hours after injection, approximately half of the parenchymal cells show signs of necrosis; after 120 hours, the liver restoration is complete. The changes occurring during the course of regeneration are not recorded here, but rather the results of this regeneration. Small pieces of the livers were fixed in acetic alcohol, embedded in paraffin, and sectioned at 15 micra. The Feulgen reaction was used to classify nuclei as to DNA content.

The classification of nuclei into polyploid (DNA) classes was made by visual comparison of whole, or nearly whole, Feulgen-stained nuclei. This method is based upon experience with photometric analysis and, like the latter, cannot

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distinguish between nuclei which have doubled the nucleic acid content in premitotic synthesis, and those which are permanent polyploids. For this reason, the study has been confined to livers that have completed mitotic activity incidental to regeneration (120 hours after poisoning). The accuracy of this method was shown by checking 100 selected nuclei with the photometric method. However, the reproducibility of the percentages of the three classes is not great when only 100 nuclei are considered, due to lack of randomness of their position in the liver, for example diploid nuclei frequently appeared grouped together. Therefore sampling of a larger number of nuclei, at least 500, chosen at random from a larger area was necessary for a reproducibility of two to three per cent in the classification by visual comparison. This was completely consistent in different pieces of a liver, and indeed, in different animals of the same age and treatment. The data on the binucleate conditions of the liver cells were also reproducible, when over 200 nuclei of a particular class were chosen at random and classified. The values for binucleates are too low due to the fact that the sectioning occasionally separates two nuclei of a binucleate cell; but they should be much nearer the real numbers than would have been found by study of thinner sections.

RESULTS

The data, presented in Table I, indicate that the percentage of diploid nuclei decreases rapidly during the growth of a normal rat and that following liver regeneration in a eight-week or older animal the diploid nuclei virtually disappear. The number of binucleate cells with two diploid nuclei is not presented, since in over 40 livers examined in this Wistar strain of rats, these diploid nuclei were almost exclusively in binucleate cells. The percentage which appeared to be in mononucleate cells, never more than three per cent, may have been due to separation by the sectioning process. The octoploid nuclei were too infrequent and too large to allow accurate determinations of the proportion present in binucleate cells. In the fourth column in Table I are recorded the percentages of cells with tetraploid nuclei that are binucleate; these clearly show an inverse relationship to the proportion of octoploid nuclei (Column 3). Under various conditions of age and treatment, all the livers show either (a) a low percentage of octoploids (less than five per cent) and a relatively high proportion of binucleate cells with tetraploid nuclei, or (b) a relatively high proportion of octoploids (over ten per cent) and infrequent binucleate tetraploids. The only exceptional case is that five days after five injections of carbon tetrachloride, where the proportion of 4N binucleate cells is higher than expected. Since there is an indication that the number of tetraploid binucleates is lower after ten days, it may be that cell division following mitosis is delayed rather than inhibited by the successive five injuries. The one exceptional individual with 16 per cent diploid nuclei possibly shows that new parenchymal cells may be formed from the bile capillaries, as Fishback postulated (11). It is clear that the polyploid frequencies seem stabilized after one carbon tetrachloride injection of eight-week old rats, so that repeated injury and regeneration cause no marked increase.

TABLE I
Polyloid nuclei and binucleate cells in livers of rats

	% 2N	% 4N	% 8N	% 4N Binucleates
<i>Normal Rats</i>				
3 weeks old	75-82*	18-24	less than 1%	20-24
8 weeks old	18-24	72-78	1-3	18-24
20 weeks old	10-15	80-88	1-5	15-20
<i>120 hours after CCl₄</i>				
3 weeks old	57-63 (36)	36-42 (63)	1-2 (1)	18-24 (26)
8 weeks old	1-4	84-88	11-13	2-5
20 weeks old	0-2	86-90	10-15	2-5
<i>After repeated CCl₄†</i>				
3 times, after 5 days	0-3	86-89	8-12	3-5
3 times, after 10 days	1-2	84-86	10-14	1-4
4 times, after 5 days	0-2	84-86	12-15	3-4
4 times, after 10 days	2	88	10	4
5 times, after 5 days	0-5 (16)	82-87 (74)	12-18 (10)	11-21 (13)
5 times, after 10 days	0-2	78-80	18-20	5-17

* The range of percentages given is that found in at least four individuals; when one individual diverged widely from the others, that value is given in parentheses. At least 500 nuclei were classified in each individual.

† The first injection of CCl₄ was given to eight-week old animals, the succeeding injections were made after ten day intervals. The times given are after the final injection.

CONCLUSIONS

The results described in this paper are in good agreement with those of many workers, showing a shift to higher polyploid nuclei with age. The eventual almost complete disappearance of the diploid class of nuclei coupled with the fact that almost all diploid nuclei prior to their disappearance are found in binucleate cells strongly supports the hypothesis that fusion of two nuclei within a cell results in a nucleus of double the chromosome number. Also, the inverse relationship between the percentages of binucleate cells with tetraploid nuclei and the octoploids is highly suggestive of a conversion of one to the other. That nuclear fusion occurs at mitosis rather than at interphase is suggested by the fact that the shift to higher polyploids takes place at a time when there are many mitoses. Also, our observations confirmed those of Beams and King (5), that while nuclei in binucleate cells enter prophase together, no cells are observed with two mitotic spindles. Additional support for this hypothesis is the stability of the polyploid frequencies after one carbon tetrachloride injury; since the percentage of binucleate cells is then very low, a further shift to higher polyploids would not be expected.

The third hypothesis mentioned in the introduction, that of endoploidy, while accounting for polyploid formation in insects and plants, seems a less likely explanation for liver growth and polyploidy in the rat. Leuchtenberger *et al.* (8) suggested, without cytological evidence, that the appearance of liver

polyploidy that follows administration of pituitary growth hormone to dwarf mice was a result of endopolyploidy. Later Swartz (9) invoked this same explanation for polyploid increase during human liver growth, and cited as evidence the fact that extensive growth occurred while mitotic activity was very low. There seem to be two possibilities of reconciling these last observations with the present results. First, mitoses may actually have occurred but been missing when the liver was studied, since post mortem material was used interchangeably with fresh liver; or second, the liver growth, estimated only as increase in wet weight, may have been predominately cytoplasmic rather than nuclear.

The results presented here agree well in principal with those given by Sulkin (7) on the effect of partial hepatectomy on the frequency of polyploid classes and binucleate cells. The actual numbers disagree, probably because of differences in technique, (his use of eight micra sections greatly reduced his binucleate frequency) and of differences in the strain and the feeding of the rat studied. The results of Heizer (12) on the consequences of thioacetamide poisoning of rat liver are markedly different in that a high degree of polyploidy occurs which is followed by a return to the normal proportions.

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NOTES ON THE EARLY MODERN HISTORY OF LUPUS ERYTHEMATOSUS

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A recent study of the early modern literature of lupus erythematosus has brought to light a degree of confusion which is astonishing even to the practised scholar. As an aid to clarification the following notes are submitted.

One of the earliest relevant documents is the curious textbook by Cazenave and Schedel. This work is the first link in the concatenation of errors and difficulties, since, in accordance with a custom occasionally practiced in France, the name of the (senior) author, Pierre-Louis Alphée Cazenave, is not given in full on the title page. The title page of the book reads as follows:

Abrégé Pratique des Maladies de la Peau, D'Après les Auteurs les Plus Estimés, Et Surtout D'Après Des Documents Puisés Dans Les Leçons Cliniques De M. Le Docteur Biett, Médecin De L'Hôpital Saint-Louis. Par Alphée Cazenave Et H. E. Schedel, Docteurs En Médecine, Anciens Internes De L'Hôpital Saint-Louis, Etc., Etc. A Paris, Chez Béchét Jeune . . . 1828.

Cazenave's full baptismal name, Pierre-Louis-Alphée Cazenave, is given correctly by some works of reference (1) and appears in the confusing abbreviated form in others.

The first edition of the textbook by Cazenave and Schedel (2) includes a section on erythema (pp. 4-9), in which are discussed such entities as erythema papulatum, erythema nodosum and variant forms. A later section of the same textbook deals with lupus (pp. 384-410). Of this disease the authors recognized three varieties: *darte rongeante qui détruit en surface* (pp. 386-389), *darte rongeante qui détruit en profondeur* (pp. 389-392), and *darte rongeante avec hypertrophie* (pp. 392-394).

In the *second* edition of their textbook (3) (pp. 9 and 10) Cazenave and Schedel introduced the following new material into the chapter on erythema:

M. Biett a décrit une autre variété bien remarquable, à laquelle il a donné le nom d'*érythème centrifuge*, et qui ne s'est présentée que très-rarement à son observation. Nous l'avons vue deux ou trois fois au Dispensaire de l'hôpital Saint-Louis.

Cet Érythème, qui jusqu'alors s'est présenté surtout chez des jeunes gens, et principalement chez des femmes, jouissant d'ailleurs d'une belle santé, paraît avoir pour siège spécial le visage . . .

In the *third* edition of the textbook by Cazenave and Schedel (4) the same description of *érythème centrifuge* is included, with very slight textual alteration (pp. 11 and 12).

Greatly to the exasperation of historians and bibliographers there are *two* fourth editions of the textbook. In one (5) the authors are given as Cazenave

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and Schedel. In the other (6) the authorship is reversed, viz. Schedel and Cazenave. In all other respects—prefatory material, text, date, publisher, and even advertisements—these two fourth editions are identical, page for page and word for word. In both fourth editions the preface is signed Alphée Cazenave et H. E. Schedel. In both fourth editions (page 66) the statement about M. Biett and his centrifugal erythema is included, with almost no modification. As in previous editions, the description forms part of the section on erythema.

In the article on erythema which he contributed to the *Dictionnaire de Médecine* (7), Cazenave made the following statement (loc. cit. pp. 252 and 253):

Érythème centrifuge.—M. Biett a décrit pour la première fois une troisième variété plus remarquable, à laquelle nous conserverons le nom de *centrifuge* qu'il lui a donné. Cet érythème est rare, et nous n'en avons vu, avec M. Biett, que deux ou trois exemples, quand, d'après ses leçons cliniques, nous en esquisâmes quelques traits en 1830 et 1833 (*Abrégé pratique des maladies ladiées de la peau*, 1^{re} et 2^e édit.).

In this reference to his own writings Cazenave made two errors: (a) *érythème centrifuge* is not mentioned in the first edition of the *Abrégé pratique*, and (b) the first edition of the *Abrégé* was published in 1828, not 1830.

Cazenave's statements, both those in the second and subsequent editions of his textbook as well as the passage just quoted from the *Dictionnaire de Médecine*, imply that Biett's description of *érythème centrifuge* was transmitted orally. This inference is supported by the official obituary notice of Biett (8), which was published in 1840. No written description of *érythème centrifuge* by Biett has thus far come to light.

At a meeting which was held at the Hôpital Saint-Louis on June 4, 1851, Cazenave presented several cases of Biett's centrifugal erythema. The account which was published in the *Annales des Maladies de la Peau et de la Syphilis* (9) bears the significant title LUPUS ÉRYTHÉIMATEUX (*Érythème centrifuge*). The title alone shows very clearly that in Cazenave's opinion the disease which Biett had described orally was the same as lupus erythematosus. The text reads as follows (10):

Cette maladie, que Biett avait signalée le premier sous le nom d'*érythème centrifuge*, est une variété du lupus.

Sans entrer dans des considérations générales sur le lupus, M. Cazenave croit devoir présenter quelques considérations sur cette variété curieuse qu'il appelle le *lupus érythémateux*.

It seems probable that Cazenave regarded the presence of cicatrization as a reason for classifying centrifugal erythema as a variety of lupus.

As great a dermatologist as Jadassohn (11) found difficulty in identifying and classifying the conditions included in the earlier depictions of lupus erythematosus. Jadassohn's opinion will receive the support of anyone who has the hardihood to seek and examine the original texts.

It is now necessary to consider the contribution of Hebra, who is widely but incorrectly credited with the first description of lupus erythematosus (12).

Hebra's supposed priority has become traditional in the literature and rests on the following reference:

Hebra, F.: *Zeitschrift der k. k. Gesellschaft der Aerzte zu Wien*, Bd. 1, p. 40, 1845.

This reference, with minor variations, is given by Kaposi (13), by Jadassohn (14), and many more recent writers. Kaposi, in fact, not only gives the reference but supports it by an excerpt from the writings of Hebra (15):

Unter dem Namen "Seborrhoea congestiva" hat zuerst Hebra im Jahre 1845 eine bis dahin von keinem Autor näher bezeichnete Hautkrankheit in folgender Weise beschrieben:

"Seborrhoea congestiva, die meines Wissens nirgends der Natur gemäss beschrieben, und höchstens von Fuchs unter dem Namen Seborrhoea adultorum . . ."

The diligent reader who pursues the traditional reference to Hebra's article in the *Zeitschrift der k. k. Gesellschaft der Aerzte zu Wien* for 1845 (16) discovers: (a) that Hebra's article was published in three instalments, (b) that the first instalment begins on page 34, not page 40, (c) that page 40 discusses the excessive production of sebum in the presence and in the absence of congestion, (d) that the passage reproduced by Kaposi (17) and alleged to be an excerpt from Hebra's article actually does not occur in it, (e) that the term "Seborrhoea congestiva" occurs not in the text on page 40 or elsewhere, but in a classified synopsis given in the last instalment of the article, on page 223.

Inasmuch as Hebra's description of seborrhoea congestiva is so widely mentioned as a *locus classicus*, a persistent search was instituted. The description was finally discovered in Canstatt and Eisenmann's *Jahresbericht* (18). The elusive passage, which so many have cited but so few have seen, is as follows (19):

Seborrhoea [sic!] congestiva, die meines Wissens nirgends der Natur gemäss beschrieben und höchstens in *Fuchs* unter dem Namen Seborrhoea adultorum oder in *Rayer* als fluxus sebaceus oder endlich von *John Erichsen* in *London med. Gaz.* November 1845 oberflächlich abgehandelt wird. Ich finde mich deshalb bewogen, aus meinem mehrwähnten Aufsaze S. 40²⁰ die betreffende Stelle hier zu widerholen:

Man erblickt beim Beginne dieser Krankheit meist im Gesichte [sic], an dem Wangen und der Nase in einer einem Schmetterlinge nicht unähnlichen Ausbreitung [sic]—auf geröthetem nicht infiltrirtem Grunde die mit ihrem Secrete erfüllten Mündungen der Talgdrüsen in Gestalt weiser nicht hervorragender Punkte . . .

In this passage, taken from the article in the Canstatt-Eisenmann *Jahresbericht*, Hebra was being careless. Although a hasty perusal of the quotation leads the reader to think that Hebra was repeating (presumably *verbatim*) a statement made in the *Zeitschrift*, in actual fact Hebra was really amplifying the account given in the *Zeitschrift*. It is the amplified version which introduces the famous simile of the butterfly and which constitutes the classic description of congestive seborrhoea.

An article by Kaposi (21) provides at once the probable clue to this annoying

bibliographic tangle. Kaposi's important article opens with the following statement:

Die ursprünglich im J[ahre] 1845 von Hebra als Seborrhöea congestiva beschriebene, schon früher von *Biett* unter dem Namen des Erythème [sic] centrifuge gekennzeichnete, ganz eigenthümlich geartete Hautaffection . . .

To this passage the following double footnote is affixed (22):

Zeitschr. d. k. k. Ges. d. Aerzte. 1845. B 1, p. 40. Canstatt's Jahresber. 1845. p. 226.

As I have already indicated, it is not the *Zeitschrift* but the *Jahresbericht* which contains the real description of the disease.

In previous paragraphs of this essay it was shown (a) that Biett called attention to a dermatosis which he named *érythème centrifuge*, (b) that Biett probably left no written description of this disease, (c) that Biett's pupil Cazenave described the disease, with proper acknowledgement, in the second (1833) but not in the first (1828) edition of his textbook, (d) that Hebra in 1845 named and briefly discussed a dermatosis designated as seborrhoea congestiva (16), (e) that Hebra (18) published an amplified description of seborrhoea congestiva in 1846, and (f) that Cazenave (9) in 1851 changed the designation *érythème centrifuge* to *lupus érythémateux*.

In his famous *Atlas der Hautkrankheiten* (23) Hebra cites the textbook by Cazenave and Schedel and states that it contains no mention of *érythème centrifuge*. It is clear from his footnote (24) that Hebra had used the first edition of Cazenave and Schedel, whereas the disease made its debut in the second edition of that textbook. Hebra thereupon erroneously concluded that Cazenave's *lupus érythémateux* was not *érythème centrifuge* but *darte rongeante qui détruit en surface*, a condition which is described in the first edition of Cazenave and Schedel (25) in the section dealing with lupus. In his atlas Hebra adopted the designation *lupus erythematosus* and devoted two magnificent plates (26) to the portrayal of the disease. It is greatly to be regretted that on one of these plates (27) the title is misspelled *Lupus Erythematosus*.

The student who follows the development of the concept of *lupus erythematosus* must sooner or later reach the name of Kaposi, since it was apparently this great dermatologist who first recognized the existence of an acute form of *lupus erythematosus* (28). An attempt to investigate the development of Kaposi's thinking on the subject of lupus—and other diseases—encounters the bibliographic difficulty that Kaposi changed his surname. His earlier writing appeared under the name of Moriz Kohn (29). The transition can be seen in the second volume of the *Lehrbuch der Hautkrankheiten* (30). In this treatise the text from pages 47 to 192 appears under the name Moriz Kohn. The text from page 193 onward appears under the name "Dr. Kaposi (Moriz Kohn)." A footnote on page 193 says:

Unser geehrter Mitarbeiter, Herr Dr. Moriz Kohn hat diesen seinen in der wissenschaftlichen Welt wohlbekannten Namen in "Kaposi" umgeändert. Der Verl.

While this change is well known to older students of dermatology and medicine, younger investigators are often found to be unaware of it.

The term *lupus erythematoses* occurs in an article by Moriz Kohn (Kaposi) (21) to which reference has already been made. In this article the word *erythematoses* is used twice (p. 33 and p. 40), apparently as a variant form having no distinctive signification. In the same article the adjective *erythematosus* occurs repeatedly.

In the foregoing pages an attempt has been made to unravel the unbelievably intricate tangle of fact and error in which the early modern history of lupus erythematosus is involved. The pathological anatomy and physiology of the disease are not less intricate than the history. Pathologists and clinicians who undertake to discover the cause and pathogenesis of lupus erythematosus would be well advised to start by attempting to define the concept which they seek to study. That the concept of lupus erythematosus has undergone modification during the last eleven decades is a truth which becomes evident only by application of the historical method. It is hoped that the present essay will be of assistance to those who seek to understand the way in which the concept and hence the problem of lupus erythematosus has changed in the course of time.

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GRANULOMATOUS INFLAMMATION OF THE KIDNEYS

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Granulomatous inflammation of the kidneys has been described by numerous observers (1-10). Various clinical syndromes (2, 9) have been recognized. However, in all, the renal manifestations have accompanied lesions of widespread nature. The extrarenal organs and systems have revealed granulomata and vascular lesions similar to those noted in the kidneys. In the three cases forming the basis of this report, the renal lesions predominated. Accompanying extrarenal vascular or extrarenal granulomatous lesions were so rare that numerous sections had to be cut and studied before they were found. In one case the renal changes appeared to be the only demonstrable lesions.

Case I

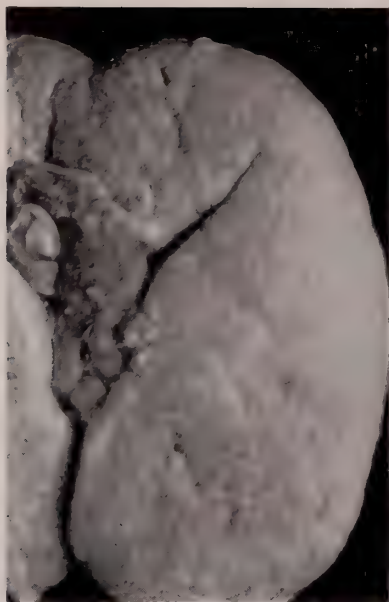
Mrs. R. S., a 61 year old white Hebrew female, was admitted because of vomiting of six months duration. The patient began to complain of left parietal headache about a year before her admission to the Maimonides Hospital. At about the same time, she began to have severe bilateral epistaxis. There was no other evidence of a bleeding tendency. Six months later, intractable vomiting occurred after all meals. It was unassociated with pain, hematemesis or melena. Marked weight loss was now noted, approximately 40 pounds, since her illness began. Her last weight was about 150 pounds; she now weighed $111\frac{1}{2}$ pounds. The patient was admitted to a hospital in another state. There, chronic bilateral suppurative otitis media and atrophic rhinitis were found. A catheterized specimen of urine revealed a specific gravity of 1.015; a trace of albumin; no casts; and 1-3 WBC and RBC per high power field were also noted. The blood revealed 7.4 grams per cent of hemoglobin with 2,500,000 RBC per cu. mm.; the WBC and differential counts were normal. Eosinophilia was not found. Chest and gastrointestinal x-Ray examinations were reported as essentially negative. There was no history of hypertension. The patient had, within the past few months, begun to complain of hesitancy and dysuria, but no hematuria.

At the Maimonides Hospital, the patient's pulse was 80 per minute and regular. Her blood pressure was 160/80; temperature was normal. She was cachectic, sallow and very pale. A small blood clot was found in her left nasal passage; no other nasal changes were noted. Other than a short systolic blow at the apex, the thorax revealed no changes. The abdominal examination revealed no abnormal findings.

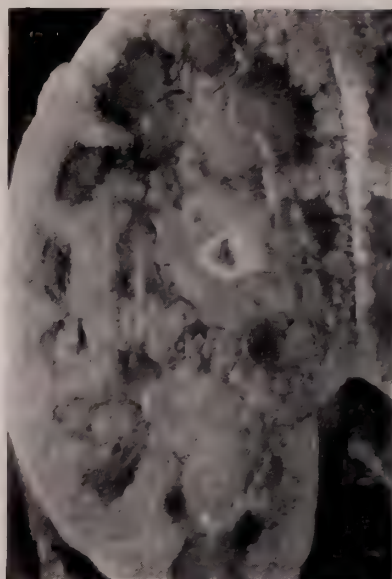
Admission blood count revealed hemoglobin, 2.5 grams per cent and 1,170,000 RBC per cu. mm.; WBC, 19,000 per cu. mm. with 20 per cent stab., 77 per cent seg., 3 per cent L., 3 per cent M.; platelets, 320,000 per cu. mm.; reticulocytes, 0.1 per cent. Urine: specific gravity, 1.010; albumin, 1+; sugar and acetone, negative; 15 RBC hpf; clumps of WBC; casts were not found. Blood chemistry revealed glucose, 105 mgm. per cent; urea N., 84 mgm. per cent; creatinine, 7.6 mgm. per cent; T. P., 5.3 gm. per cent; A., 2.2; G., 3.1; phosphatase, 13.0 (K.A.); chlorides, 90.4, mEq l; CO_2 , 10.6 mEq l; cholesterol, 175 mgm. per cent; calcium, 7.6 mgm. per cent; phosphorus, 6.3 mgm. per cent. Stool was guaiac negative.

The patient's condition deteriorated progressively, as her azotemia increased. During one week in the mid-portion of her stay, 2650 cc. of fluid were removed from her left chest. Neither tumor cells nor acid fast bacteria were found. At this time, the E.C.G. revealed "signs suggestive of myocardial damage. The absence of Q waves arouses the suspicion of pericardial involvement, in view of the history of uremia". On the 19th day of her hospital

From the Department of Laboratories, Maimonides Hospital, Brooklyn, N. Y.



A



B

FIG. 1A. Case I. Kidney surface.

FIG. 1B. Case I. Cut surface revealing cortical involvement.

stay, "a complete and marked perforation of the nasal septum" was noted for the first time. 2300 cc. of whole blood maintained the hemoglobin at 8 grams per cent and the RBC at 2,540,000 per cu. mm. Retrograde pyelography revealed no abnormal findings.

A pericardial friction rub became audible ten days before death. Convulsions occurred for the first time one week before death and the patient became stuporous. The temperature ranged between 99° and 101°; cough accompanied by grayish-yellow sputum and diffuse rhonchi were noted throughout the chest. The patient expired 40 days after her admission to the hospital. The final diagnosis was chronic pyelonephritis.

Gross. The body weighed 90 pounds, appearing markedly cachectic. Brown crusts covered the nares. Approximately 50 cc. of clear, yellow fluid was found in each pleural cavity. The right and left lungs weighed 535 and 310 grams, respectively. No areas of consolidation or granularity were noted. Both lungs revealed normal markings and color. Droplets of pus could be expressed from the smallest bronchi on the cut surfaces. Similar material was noted on the intact mucosa of the larynx, trachea and major bronchi. A calcified lymph node was found in the tracheo-bronchial area. The other nodes were not enlarged.

The pericardial sac revealed fibrinous pericarditis. The heart weighed 370 grams. The coronary vessels revealed only minimal sclerosis. No areas of infarction were noted. Thrombotic material was attached to the mural endocardium of the right auricular appendage, the right ventricle and the apex of the left ventricle. Valvular changes were not found.

The kidney capsules were thickened, but stripped with ease revealing a surface peppered with yellow-gray discrete and confluent granules (Fig. 1, A, B). Virtually no areas of uninvolved surface were noted. The right and left kidneys weighed 210 and 220 grams, respectively. Cut sections revealed a sharp differentiation between cortex and medulla. The former is widened, accentuating the diffuse granularity noted on the surface. As on the capsular surface, the cortex reveals a diffuse involvement with only minute areas showing remains of normal cortex. Strikingly, the medulla, by contrast, presented a completely normal appearance. The pelvis, ureters and bladder revealed no changes.

Bacterial cultures, animal inoculations and, subsequently, special stains revealed no organisms. Tubercle bacilli were not found.

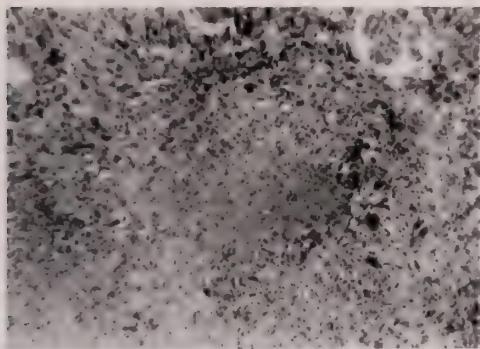


FIG. II. Case I. Tuberculoid granuloma, kidney.

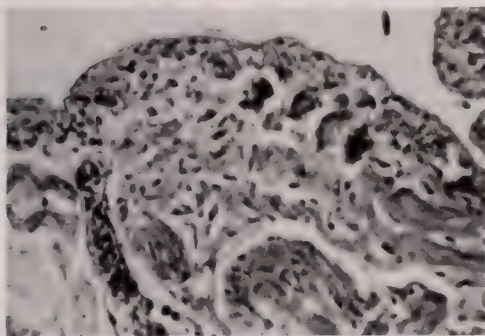


FIG. III. Case I. Mucosal granuloma, bronchus.

The liver and spleen weighed 1380 and 235 grams, respectively. No abnormalities were noted.

The gallbladder, pancreas, adrenals, gastrointestinal tract, thyroid, parathyroid and the uterus, with its adnexae, were normal.

Microscopic. The most profound changes were noted in the kidneys (Fig. II). Granulomata in varying stages of development, from cellular infiltration through necrosis to organization, were noted in the cortex. The medulla revealed no granulomata. The granulomata in the cortex appeared around or in juxtaposition to glomeruli. The glomeruli revealed single loop, as well as total glomerular changes. Conglutination and necrotization of loops, capsular proliferations (crescents), periglomerular proliferations and granulomatous inflammation were noted.

The epicardium revealed an organizing fibrinous and exudative subacute inflammation. Granulomata were not found. The myocardial fibers and interstitium revealed no essential changes. The endocardial surfaces, excluding the normal valvular endocardium, revealed subendothelial accumulations of mineralized eosinophilic debris, giving a positive van Kossa stain. Bacterial organisms were not found. Mural thrombi were also noted, in areas, in direct continuity with the subendocardial material.

The mucosa of rare bronchi revealed small granulomatous collections with histiocytes, lymphoid cells and multinucleated giant cells of the "foreign body" type (Fig. III). Necrosis was not found. Minute foci of acute broncho-pneumonia and pulmonary edema were scattered throughout both lungs, although sections from the larynx and trachea revealed no changes. Tissue from the nasal mucosa and septum was not examined.

The final diagnosis, after the microscopic study was: Granulomatous nephritis, etiology unknown; rare bronchial granulomata; mural thrombi, heart; pericarditis, uremic; azotemia, clinical; pulmonary edema; minimal acute broncho-pneumonia.

Case II

Mrs. R. R., a 72 year old white Hebrew widow, was admitted to the hospital from the clinic because of anemia and increasing elevation of her fasting blood sugar. Her first admission occurred in 1931 when a radical mastectomy was performed for duct cell carcinoma of the breast. (A review of the slides confirmed the original diagnosis.)

The patient was a known diabetic since 1943. At the end of ten years, anorexia and progressive weight loss were noted. With the development of symptoms, 10 units of PZI were substituted for the insulin, whereupon she had a rash and pruritus at the injection site. A special PZI then replaced the regular insulin. Increasing difficulty in controlling the diabetes was noted. Varying doses and forms of insulin (including special insulin) were tried because of severe local reactions. From December 1955, to the time of admission, April 11, 1956, the patient lost 18 pounds. She was placed on 25 units of another special PZI. Additionally, a progressive weakness and tremulousness developed. The latter was noted on both voluntary and involuntary motion. She was unable to fend for herself. Progressive swelling of the ankles and feet made it difficult for her to walk or move her legs. Upon referral to the neurology clinic, treatment with reserpine was instituted. Depression of severe degree supervened and the treatment was discontinued.

In December, the patient developed a "cold", lasting several weeks. The temperature rose to 101°. No chills were noted. Pounding headaches developed on the left side. Cough, productive of yellow sputum, was noted. Since then, the symptoms noted above, weight loss, weakness, tremulousness and difficulty in walking, progressed. Nausea and vomiting developed before admission, as did orthopnea (two pillow) and dyspnea.

Clinical improvement resulted after therapy. About one to two years prior to admission, she was told that she had a systolic hypertension (180 mm. Hg). A diastolic pressure of 90 mm. Hg was noted on a number of occasions.

Examination revealed B.P., 180/100; T., 97°; P., 100 per minute and regular; R., 28 per minute. The patient appeared markedly chronically ill and in acute distress. The right breast was absent. The mucous membranes were pallid. The cardiac examination revealed no essential changes. Minimal sacral and leg edema was noted. Marked swelling was present in the right arm (post-mastectomy lymphedema). Diminished breath sounds and moist rales (inspiratory and expiratory) were heard at both bases.

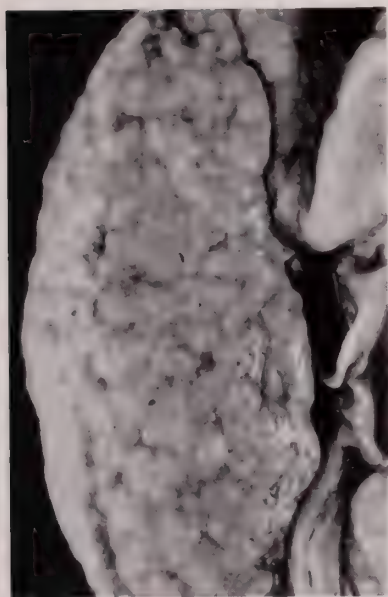
The abdominal, rectal and vaginal examinations revealed no abnormalities. The provisional diagnoses were: diabetes mellitus; anemia, secondary to uremia; hypertensive arteriosclerotic heart disease, Class IV.E. The possibility of kidney disease associated with diabetes was also considered. The patient received two units of packed R.B.C.

On the day following admission, while an E.C.G. was being taken, the patient lapsed into coma and expired. The tracing revealed signs suggestive of left ventricular strain.

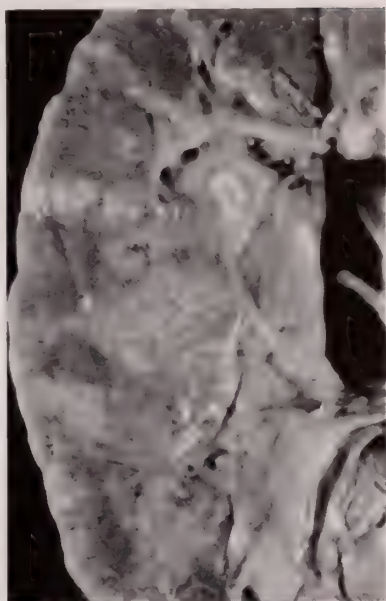
Laboratory examinations during her two day stay showed: Urine specific gravity, 1.010 with 1+ and 2+ albumin; glucose and acetone, negative; occasional WBC and granular casts per high power field; E. Coli was cultured. Blood: Hemoglobin, 5.8 grams per cent; RBC, 2,100,000 per cu. mm.; WBC, 17,700 per cu. mm.; 74 per cent seg., 15 per cent band, 8 per cent L., 3 per cent M. The stool was guaiac negative. Blood chemistry: Sugar, 212 mgm. per cent; urea N., 87 mgm. per cent; creatinine, 4.5 mgm. per cent; T.P., 7.2 gm. per cent; A., 2.2; G., 5.0; CO₂, 20.8 mEq/l; chlorides, 97 mEq/l; Na, 136 mEq/l; K, 5 mEq/l; ieterus index, 5; Ca, 8.4 mgm. per cent; P, 7.9 mgm. per cent. A sternal marrow examination revealed a normoblastic picture.

Gross. With the exception of the kidneys, all of the organs revealed no essential changes. The lungs, right and left, weighed 680 and 550 grams, respectively. The essential picture was that of edema and congestion.

The heart weighed 320 grams. The left ventricle was 1.5 cm. in thickness revealing a slight bulge in the subaortic area of the outflow tract. The valves were essentially normal. Thickening and calcification of the coronary arteries were noted, although neither marked narrowing nor occlusions were noted.



A



B

FIG. IV.A. Case II. Kidney surface.

FIG. IV.B. Case II. Cut surface.

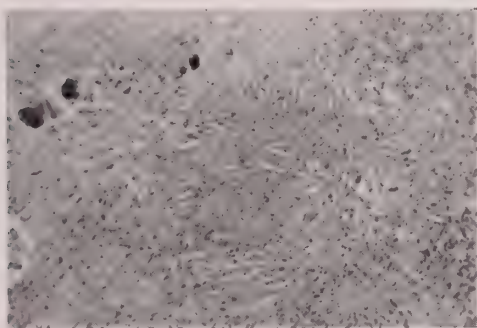


FIG. V. Case II. Glomerulus and juxtaglomerular granuloma.

The liver and spleen weighed 1190 and 65 grams, respectively. The pancreas and adrenals were also normal in appearance.

Each kidney (Fig. IV, A, B) weighed 155 grams. The capsules stripped with great difficulty revealing creamy-yellow, finely and coarsely granular surfaces. The cut surfaces revealed discrete and confluent granularity with the creamy-yellow color noted above. The cortico-medullary junctions were sharp. In this zone, an infrequent minute area of apparently uninvolved cortical tissue was noted. The medulla was entirely normal except for pronounced congestion. The pelves, ureters and bladder were normal. Smears, cultures and animal inoculations revealed no organisms, especially tuberculosis.

The uterus and adnexae revealed no changes other than a small, pedunculated, subserous myoma (1 cm. diameter) and atrophic ovaries.

Microscopic. The kidney sections revealed a diffuse seeding of the cortex with miliary granules of approximately equal size. The granules appeared around or adjacent to glomer-

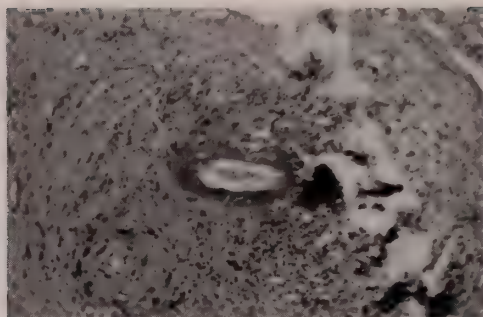


FIG. VI. Case II. Necrotizing angiitis, ovary. One of two vessels found in both ovaries.

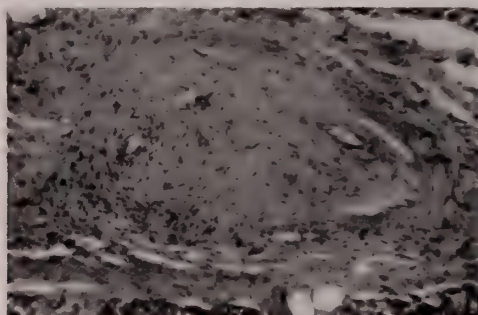


FIG. VII. Case II. Healed aneurysm, pancreas.

uli. The granules varied from acute necrosis, simulating caseation, to fibrous, scarred granulomata. The cellular content consisted of lymphoid cells, histiocytes, leucocytes (infrequently eosinophilic) and multinucleated giant cells, both foreign body and Langhans (Fig. V).

The glomeruli revealed exudative and proliferative changes. Conglutination of loops, necrotization of individual loops and total glomeruli, crescent formation, at times involving the entire capsule in annular fashion, and thrombosis of loops were noted. The involved glomeruli were found in conjunction with the granulomata described above. In many instances they appeared in the granulomatous centers. In others, they were present at or adjacent to the periphery of the granulomata. Tubular continuity disruption and atrophy were prominent. Vascular sclerosis was present. However, necrotizing vascular lesions were not found. The medulla was uninvolved.

One ovary and the pancreas contained vessels showing changes. Two small arteries in the ovary (Fig. VI) revealed fibrinoid necrotization of the intima and media with a perivascular collection of leucocytes, histiocytes and lymphoid cells. Few eosinophilic leucocytes were found.

The pancreas revealed a small interlobular artery with a healed, recanalized aneurysm (Fig. VII). No other organ changes were found.

The final diagnoses were: Granulomatous nephritis, etiology unknown; rare necrotizing angiitis, ovary; healed microaneurism, pancreas; diabetes mellitus, clinical; allergy to insulin, clinical; hypertension, clinical; uremia, clinical.

Case III

Through the courtesy of Dr. Alvin J. Cox of Stanford University School of Medicine, I have obtained kidney sections from a 60 year old Mexican female, whose disease of eight

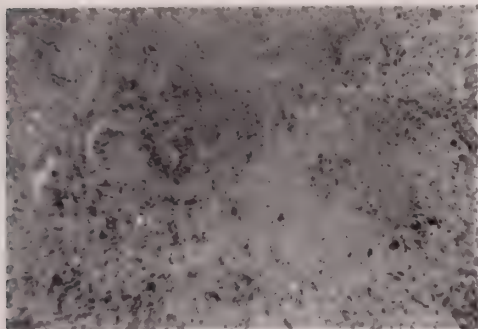


FIG. VIII. Case of Cox. Glomerulus with juxtaglomerular granuloma.

months duration was always obscure. There was pain and swelling of the fingers, rapidly shifting to other parts of the body, associated with chills and fever, severe uveitis, moderate anemia with mild leucocytosis and, finally, rapidly progressive renal impairment and death in uremia.

"Your case", wrote Dr. Cox, "presented the same curious localization of the lesions to the cortex of the kidney. No granulomatous lesions were found outside of the kidneys. Careful study using special stains and animal inoculations disclosed no causal agent.

"We were unable to come to any satisfactory conclusion regarding the nature of this disease. The most common view was that it might be related to Disseminated Lupus Erythematosus."

Subsequently, private conversations with Dr. Cox elicited the further information that no vascular lesions were observed in any of the organs.

Examination of the kidney sections revealed findings similar to those noted in the two previous cases (Fig. VIII). Although all of the changes found in the other cases were also noted in the sections studied, the impression was that more advanced organization of the granulomata was noted in this instance. Necrotizing vascular lesions were not found.

Recapitulating, the three female patients, 60, 61 and 72 years of age, were admitted with profound azotemia leading to death. The accompanying clinical features were:

Case I: Nasal septal necrosis, chronic sinusitis, otitis media, marked anemia and uremic pericarditis.

Case II: Previous mastectomy for carcinoma (25 years), diabetes mellitus, long-standing insulin allergy, hypertension and marked anemia.

Case III: Migrating polyarthritides, chills, fever, severe uveitis and moderate anemia.

In each patient, the search for a causal agent was fruitless. Special stains, cultures and animal inoculations were all negative. Intensive search was made in view of the tuberculoid character of the renal granulomata. In our cases, as well as in those reported in the literature, all efforts were in vain.

The renal lesions were distinctive, varying only quantitatively: the necrotizing glomerular tufts, capsular proliferation, granulomatous periglomerulitis and juxtaglomerular and interstitial tuberculoid granulomata limited to the cortex. Vascular lesions were absent in the kidneys of each case.

In Case I, the rare bronchial granulomata and nasal septal necrosis; in Case II, the rare necrotizing angitis and healed aneurism; and in Case III, the absence

of any other morphologic changes were the outstanding accompanying changes, albeit minimal.

DISCUSSION

Granulomatous inflammation of the kidney has been described by numerous observers (1-10). However, in all of the above reports, the renal lesions were merely part of a more extensive series of clinical or pathological changes.

In a critical review of "Wegener's Granulomatosis", Godman and Churg (5) delimit the syndrome to a disease characterized by "aggressive necrotizing granulomata of the respiratory tract, generalized angiitis, necrotizing glomerulitis and, frequently, disseminated granulomata". While Wegener (9) emphasized the periarteritic lesions, many authors, including Godman and Churg (5), placed more emphasis on the granulomatous nature of the disease.

The disease in which the granulomatous changes in the nose and accessory sinuses predominate, lethal midline granuloma, has been described by many authors (11-13). Spear and Walker (11) agree with Wegener (9) that the two diseases are not related histologically. Although Godman and Churg (5) discuss the possibility of intermediate forms with lethal midline granuloma at one end of the spectrum and its generalized form, Wegener's granulomatosis at the other end.

Similarly, our case I revealed a destroyed nasal septum, rare bronchial mucosal minute granulomata and profound renal changes. Vascular changes and other visceral dissemination were not found. This may have been in transition to Wegener's Granulomatosis, although the basic triad of the syndrome were not present in their entirety.

Many cases of renal granulomatosis and necrotizing glomerulitis have been reported in conjunction with periarteritis nodosa (1, 2, 4, 7, 10). The authors have invariably stressed the importance of the periarteritic changes. Zeek, in a recent review, has emphasized the heterogeneous character of the cases designated "periarteritis nodosa". Klemperer (15) has stated, "not every necrotizing arteritis is necessarily a periarteritis nodosa". Zeek (14, 16) prefers to use the term "necrotizing angiitis" to designate the "group of vascular lesions, arterial and venous, the fully developed stage of which consists of fibrinoid necrosis and inflammatory reaction involving all three coats of the vessel walls". She recognizes five types of necrotizing angiitis: (a) hypersensitivity angiitis; (b) allergic granulomatous angiitis; (c) rheumatic arteritis; (d) periarteritis nodosa and (e) temporal arteritis. For Karsner (17) the diagnosis of periarteritis nodosa cannot be made in the absence of local eosinophilia. However, local eosinophilia may be present in the other forms of necrotizing angiitides.

In our case II, there were but three small vessels that revealed the acute (two) or healed (one) stages of necrotizing angiitis. Few eosinophilic leucocytes were noted; granulomata were not found in the perivascular areas. In fact, granulomata were found in no organs other than the kidneys. Although the paucity of such vascular lesions may belie their importance, in other well-known conditions vascular or organ changes may be out of proportion to the clinical symp-

toms: In malignant nephrosclerosis, the vascular lesions may be small in number; in disseminated lupus erythematosus, especially in the pre-steroid therapy era, the renal lesions were not infrequently difficult to demonstrate. However, it would seem that the necrotizing vascular lesions were of lesser import in relation to the granulomatous renal changes and clinical picture.

It is significant, I believe, that necrotizing angitides have been produced by numerous methods: drugs (18-21), steroids (22), experimental renal ischemia or insufficiency (23), hypertension (24) and other physical, chemical and bacterial agents (14). In R. R. (case II), renal insufficiency and hypertension were present clinically.

In all of the cases, there was one common lesion, viz, the necrotizing glomerulitis, granulomatous periglomerulitis and granulomata. This was the morphologic change responsible for the death of each patient in renal failure. In the report of Godman and Churg (5), 86 per cent of the patients died in uremia. The kidneys do not present the picture of a diffuse glomerulonephritis, but rather one similar to focal necrotizing glomerulitis. It has long been believed that the Loehlein lesion of subacute bacterial endocarditis was due to a hypersensitivity mechanism.

Masugi (25) and Cavelti and Cavelti (26) have produced glomerulonephritis through antigen-antibody reactions. Mellors and Ortega (27, 28), by a micro-fluorescence method, have demonstrated the histologic site of localized gamma globulins in the active glomerular lesions of glomerulonephritis and arteritic lesions of necrotizing angitides. Granulomata are, according to Goddard (29), a characteristic "qualitative" change in focal anaphylactic inflammation. Similarly, the glomerulitis is so recognized (26-28).

It, therefore, becomes highly suggestive that the renal lesions, necrotizing glomerulitis, periglomerulitis and granulomatosis, were the result of a hypersensitivity or antigen-antibody reaction. The etiologic agent may have differed in each of the cases, but the pathogenetic mechanism and, surely, the end-result were the same.

The relationship of the glomerular to the granulomatous lesions is unknown. Forbus (30) implicates numerous agents, animate as well as inanimate, in the production of granulomata. The agents pertinent to our cases may reside in the tissue products resulting from the glomerular changes. The "rheumatic state" furnishes the most exquisite example of a granulomatous inflammation with tissue necrosis (31, 32). Although the same agent producing the granulomatous and necrotic lesion may produce the glomerulitis, it is also conceivable that another agent may be responsible for the latter. However, the morphologic age similarity of the apposed glomerular and granulomatous lesions may implicate the necrotizing glomerulitis as the precursor of the periglomerular and interstitial granulomata. The absence of vascular lesions tends to rule out an ischemic basis for the change.

An interesting feature, aside from the known hypertension over a period of years in our case II, R. R., was the presence of an allergic reaction to insulin. The patient reacted unfavorably to each of the various types of insulin necessary

for the control of her diabetes. It is known that three types of insulin allergy occur (33): (a) mild local reaction; (b) severe local reaction; and (c) generalized reaction (urticaria, angioneuritic edema, circulatory failure, asthma, arthralgia and gastro-intestinal symptoms). Insulin, a hapten, is considered weakly antigenic, although the demonstration of such antibodies is difficult (34). Lowell (35) and many other investigators have attempted to adduce such evidence. Arquilla and Stavitsky (36), by the addition of complement, have converted the hemagglutinating to a hemolytic reaction. The use of diazotized benzidine has enabled them to determine the reaction colorimetrically. They have thus been able to demonstrate antibodies to insulin.

The reaction of our patient, R. R., to insulin may be an incidental finding; however, it would be tempting to speculate about the relationship to the basic disease.

In patient III, the association of migrating polyarthritis or arthralgias with chills and fever, and the progressive renal impairment, were noted with granulomatous kidney disease. Uveitis was an added finding. In the previously reported cases (18), necrotizing vascular disease was also present. According to Cox (37), the only morphologic change was the renal cortical disease. Neither vascular changes nor granulomata were noted in the other organs.

The morphologic component common to all three female patients, between the ages of 60 and 72, was the granulomatous nephritis (glomerulitis, periglomerulitis and the juxtaglomerular granulomata). It cannot be emphasized too strongly that the morphologic identity does not imply etiologic identity.

It appears, therefore, that a host of different clinical features with morphologic counterparts—nasal sinus, middle ear infection or destruction, polyarthritis uveitis or others, unrecognized in our patients (conceivably, even insulin allergy) may be responsible for the hypersensitivity or antigen-antibody reaction in the kidney. This may result in the peculiar granulomatous nephritis seen in the three patients described above.

SUMMARY

The pathology of three cases of granulomatous nephritis has been described. Necrotizing glomerulitis, granulomatous periglomerulitis and interstitial granulomatosis, limited to the cortex, characterized the renal changes. The protean nature of the clinical manifestations and the relationship to hypersensitivity or antigen-antibody reactions were discussed.

ACKNOWLEDGMENT

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ASEPTIC NECROSIS OF THE FEMORAL HEAD

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This paper deals with several instances of aseptic necrosis of the femoral head, each case exemplifying a different basis for the underlying interference with the blood supply to the affected head. Though there are many circumstances under which aseptic necrosis of the femoral head may appear, we shall limit our discussion to its occurrence: 1) in connection with caisson disease; 2) after trauma to the hip area, without fracture and apparently without dislocation; 3) after trauma to the hip area associated with dislocation of the head; 4) without any known cause (idiopathic (?) aseptic necrosis); and 5) in connection with Gaucher's disease. The roentgenographic picture and the gross pathologic findings representing the fully evolved aseptic necrotic state and its sequelae are quite similar, whatever it may be that had induced the interruption of the local circulation. The histologic findings, too, in most cases of aseptic necrosis of the femoral head present an essentially consistent pattern, though there may be special elements in the picture as, for instance, in the case of a head in which the aseptic necrosis has followed in the wake of Gaucher's disease.

ASEPTIC NECROSIS FROM CAISSON DISEASE

Bert in 1871 was the first to describe the clinical picture of caisson disease and to advance the theory of its etiology. As is well known, this condition appears in persons who work under high atmospheric pressure (usually underground) and undergo decompression too rapidly (see Phemister (1, 2)). In a person subjected to high atmospheric pressure, excessive quantities of nitrogen accumulate in the tissues—particularly at sites where there is a considerable amount of fat. Indeed, nitrogen is taken up by the tissues high in fat in amounts up to about 5 times the amounts taken up by tissue poor in fat.

When a person who has been subjected to high atmospheric pressure is decompressed gradually, the lungs are able to ventilate the nitrogen liberated from the various tissues and dissolved in the blood, because the lungs are not deluged with nitrogen in the blood circulating through them. Under conditions of excessively rapid decompression, the lungs are not able to ventilate all the nitrogen gas presented to them. In consequence, some of the dissolved nitrogen in the blood and tissues becomes liberated as gas bubbles, and the scene is set for an attack of "the bends" and also for damage to various tissues. The liberated nitrogen gas bubbles may act as gas emboli partially or completely blocking terminal vascular channels, or may accumulate in an area in such a way as to obstruct by extravascular pressure the blood flow to that area. In either or both of these ways, ischemia and/or tissue necrosis results.

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"The bends" represent the acute manifestations of excessively rapid decompression. In the course of, or within 30 minutes after, such decompression, the subject suffers from diffuse pains. In addition, there may be convulsions as manifestations of injury to the central nervous system. Death rarely ensues, but if it does, it is due to massive pulmonary and/or cerebral gas bubble embolization. Once recovered, the subject of "the bends" may be free of clinical complaints for months or years.

Here we are concerned with the manifestations which sometimes appear later in the skeletons of subjects who have had "the bends." Specifically, some of the bones (especially long bones) may show extensive infarcts. These may be clinically silent unless one or another articular end of the affected bone is involved. However, the end of a bone may be the site of an infarct for a long time before clinical difficulties ascribable to it appear. These are mainly the consequences of collapse of the necrotic articular bone end, and the consequent evolution of the changes of an osteoarthritis.

A case in point relates to a man 40 years of age who worked under compressed air for about 19 years before suffering an attack of "the bends" in 1947. He continued to work regularly and apparently without any complaints during the ensuing year. He then began to have difficulties relating to both shoulders and hips, but continued to work. The complaints were: increasing pain, stiffness, and limitation of motion of both shoulders, both hips, and the back. In 1949 (about 2 years after the attack of "the bends") difficulties referable especially to the hip joint areas forced him to stop working and he entered our hospital for reconstructive surgery on the hip joints. The roentgenographs of the shoulder and hip areas showed considerable radiopacity in the upper ends of the humeri and femora and also the presence of in situ osteochondral fracture fragments in all 4 joint areas in question. Thus, the x-ray pictures showed the sequelae of bone infarction in the form of aseptic necrosis, collapse, and the presence of fracture fragments at the articular ends of the bones in question.

Pathologic Changes in the Right Femoral Head.—This head became available for study because it had been removed (at the head-neck junction) in connection with the substitution of a prosthesis for it. The head was abnormal in shape and also in other aspects of its external appearance. The articular surface was irregularly bumpy and showed, along part of the circumference, a deep groove where the articular cartilage was depressed. Also, the cartilage in general showed extensive yellowish-brown discoloration, and in some places a good deal of fibrilization and here and there some superficial erosion.

When the head was transected, the changes seen were even more conspicuous (Fig. 1). In particular one could note large irregular patches where the osseous tissue was strikingly yellow. As past experience has shown, the osseous tissue within such areas is completely necrotic and the intertrabecular marrow spaces are filled with calcific material. This was confirmed by microscopic study of a tissue block from such an area. In other places the spongiosa of the head appeared grayish, and in these areas in particular the osseous tissue was found densified. Such areas represent fields in which there has been a good deal of repair, any

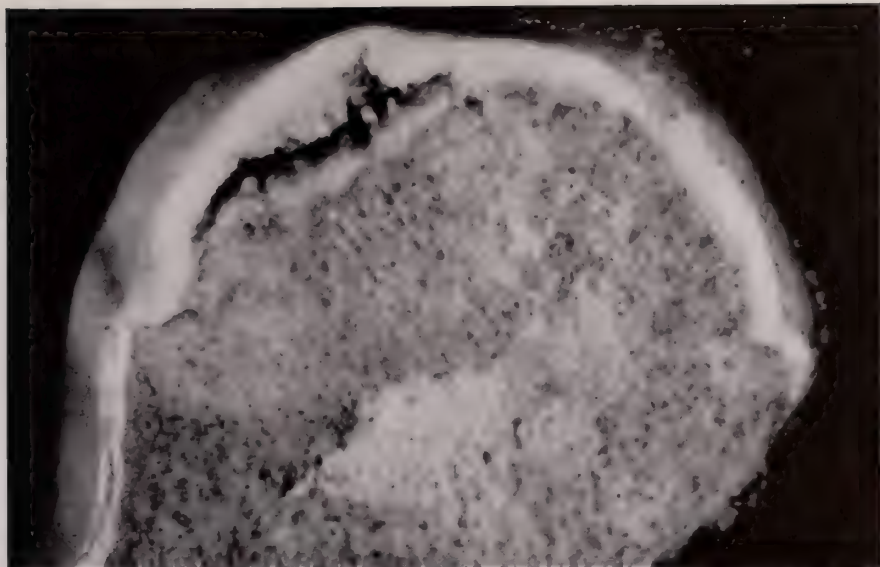


FIG. 1

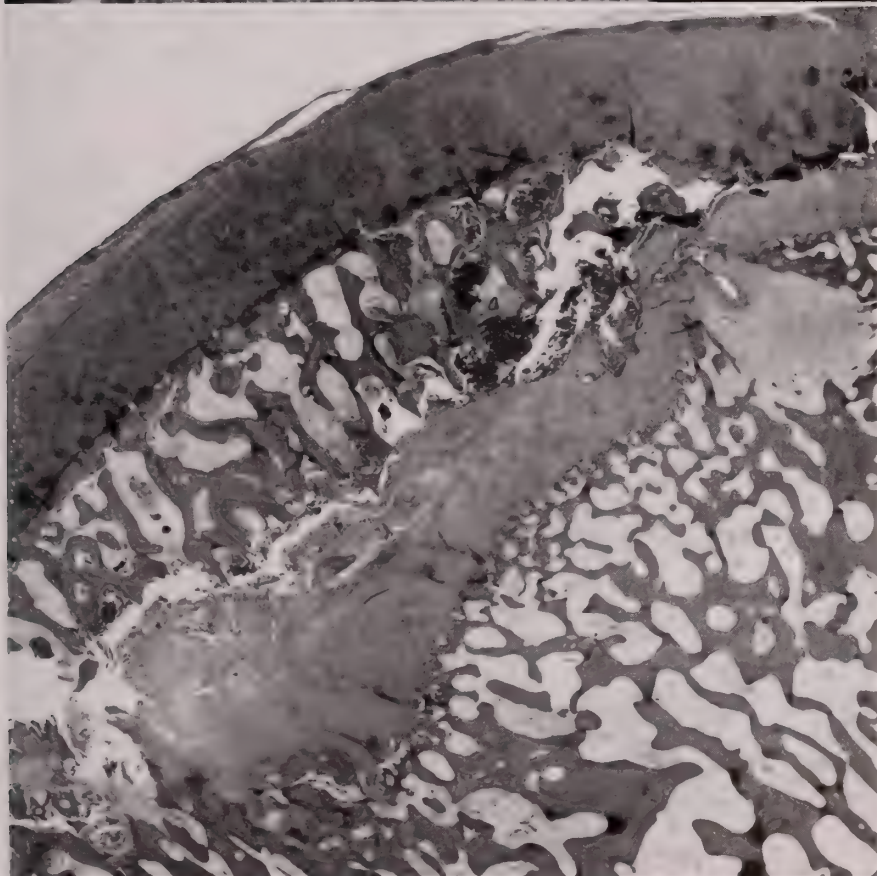


FIG. 2

FIG. 1. Photograph of the transected and substantially necrotic femoral head from a case of caisson disease. Note, above and to the left, the presence of a subchondral fracture. The osseous tissue is whitish and necrotic and is demarcated from the deeper osseous tissue by a space and a zone of fibrous tissue. (For histologic details, see Fig. 2.) Much of the rest of the head appears whitish, and the osseous tissue is, for the most part, also necrotic.

FIG. 2. Photomicrograph ($\times 10$) showing the necrotic osseous tissue to the left and above. The covering articular cartilage was viable but modified. In the area of necrosis, the marrow contains some granular detritus.

calcific detritus originally present having been resorbed, the intertrabecular marrow having undergone fibrosis, and the osseous tissue having become thickened through new bone apposition. One could also note a few small cystlike spaces spread over the cut surface.

Furthermore, the cut surface revealed in the gross the presence of an in situ osteochondral fracture (Fig. 2). In the area of the fracture a small fragment of yellowish necrotic bone which was continuous with the overlying articular cartilage had become clearly delimited and separated from the underlying spongiosa. This in situ fracture could be regarded as entirely analogous to an idiopathic (?) osteochondritis dissecans fracture fragment such as is rather commonly encountered in the lower end of the femur in otherwise healthy young subjects. Finally, at the margin of the head near the head-neck junction, one could observe, both grossly and microscopically, a well developed marginal exostosis analogous to the marginal exostoses to be seen in cases of osteoarthritis of the hip joint arising from other causes also.

ASEPTIC NECROSIS FOLLOWING TRAUMA WITHOUT FRACTURE OR DISLOCATION

Accumulating experience indicates that a subject may suffer a trauma to the hip area and come to develop aseptic necrosis of the femoral head, even if the trauma has not induced a dislocation at the hip joint or a fracture of the femoral neck. In such cases one can only speculate as to the manner in which the interference with the circulation in the femoral head came about. It might be that the trauma induced a reflex ischemia which, being prolonged, had led to devitalization of the femoral head and ultimately to its collapse.

A case in point is that of a boy 13 years of age who had fallen down some stairs (a distance of about 8 feet) about a year before his admission to our hospital. Immediately after this incident, he could not walk or put weight on his right hip. At that time he was hospitalized at another institution for about $2\frac{1}{2}$ months. We have been unable to obtain satisfactory information about that period of hospitalization. However, we have been informed that roentgenographic examination of the hip on admission to that hospital did not disclose a dislocation.

About 6 months before admission to our hospital, the boy again began to experience pain and disability relating to the hip. X-ray examination now showed flattening and mushrooming of the femoral head, within which there was a large and irregular but sharply delineated radiopaque focus undoubtedly representing necrotic osseous tissue. The radiopaque region was demarcated toward the neck by a narrow zone of relative radiolucency, and in the neck of the bone there was a roundish area of relative radiolucency measuring about 1 cm. in diameter (Fig. 3).

Pathologic Changes in the Femoral Head.—The femoral head (which had become available for anatomic study) was found flattened, in conformity with what had been seen in the clinical x-ray picture. The articular cartilage was brownishly discolored for the most part. In some places it was fibrillized, and over part of the surface it was loosened from the underlying bone. On transecting

FIG. 3



FIG. 4



FIG. 5

FIG. 3. Roentgenograph showing a necrotic and deformed femoral head in the case of a boy 13 years of age who, about 8½ months previously, had suffered trauma to the hip area, but no fracture or dislocation.

FIG. 4. Roentgenograph of a flattened, necrotic, and deformed femoral head in the case of a man 67 years of age who had incurred a posterior dislocation of the femoral head in an automobile accident about 8 months before this picture was taken.

FIG. 5. Photograph of the transected necrotic femoral head illustrated in Fig. 4. The contour of the head is flattened. A substantial part of the head appeared yellowish-white and necrotic.

the specimen one could observe that the osseous tissue of the head was abnormal everywhere. Much of it was frankly yellow and obviously necrotic. Elsewhere one could observe intermingled yellowish and grayish areas, apparently representing regions in which the necrotic osseous tissue was being repaired and replaced. Where the underlying bone was frankly and totally necrotic, the articular cartilage was separated from it. On the neck side of the specimen, small islands of epiphysial plate cartilage could still be observed.

Microscopic examination of tissue sections from this femoral head confirmed the gross findings. In the areas obviously necrotic in the gross, the spongy trabeculae were completely nonviable and the intertrabecular marrow spaces were packed full with granular detritus. In the areas in which the necrosis was less obvious grossly, there was microscopic evidence of revascularization. In these areas the spongy trabeculae were quite thick, and many of these trabeculae showed, particularly deep in their substance, nonviable osseous tissue upon which new bone had been deposited. The fragments of epiphysial cartilage plate were viable on the whole and showed endochondral ossification proceeding on the neck side of the plate. Also, there was no evidence of bone necrosis on the juxta-epiphysial side of the plate.

ASEPTIC NECROSIS FOLLOWING DISLOCATION

It is well known that in persons, especially adults, who have suffered posterior dislocation of the femoral head, the latter frequently becomes extensively necrotic. This is likely to happen even if the dislocation is immediately reduced. The necrosis in these cases follows upon the interference with the circulation in the femoral head both through tearing of the ligamentum teres and through interruption (even though temporary) of the local blood supply normally also reaching the femoral head and neck by way of the articular capsule.

A case in point relates to a man 67 years of age who had been in an automobile accident 12 days prior to admission to our hospital. He had been riding in the back seat of a car which was in a collision, but the precise mechanism of the injury to the hip was not clear. We do know that he was immediately hospitalized near the scene of the accident, that he stayed in the local hospital for several days, but that no particular treatment was given. On admission to our institution a complete posterior dislocation without fracture was observed roentgenographically in the left hip. Under general anesthesia the dislocation was reduced by manipulation.

About 8 months after the traumatic incident and reduction of the dislocation, the patient returned to the hospital complaining of pain in the hip. He stated that the pain was of about 2 or 3 months' duration and that its onset coincided with a fall. A roentgenograph taken at this second admission showed that, although the femoral head was in the acetabulum, it was deformed and a large part of it was radiopaque in accordance with the necrosis that had occurred in it (Fig. 4).

Pathologic Changes in the Femoral Head.—In this case, too, the femoral head became available for anatomic examination. The shape of the head was found

distorted and in particular irregularly conical. The articular cartilage was almost completely altered in appearance, being markedly frayed at the dome of the cone. Also, in some places the articular cartilage was found definitely loosened from the underlying bone.

In this case, too, the transected specimen showed that much of the osseous tissue of the head was yellowish in appearance. Furthermore, beneath the flattened articular surface there was a large wedge of necrotic bone which was strikingly yellow and which was delimited from the rest of the femoral head by a margin of fibrous tissue (Fig. 5). Microscopic examination showed that the osseous tissue in the wedge-shaped area in question was completely necrotic, and that the intertrabecular marrow spaces were substantially filled with granular detritus. The narrow fibrous delimiting band seen grossly separated the zone of completely necrotic osseous tissue from the deeper zone in which the marrow was fibrosed and the osseous tissue was not completely necrotic. Indeed, in many places one could find evidence of new bone apposition on trabeculae of bone which were either partially or completely nonviable.

ASEPTIC NECROSIS OF OBSCURE CAUSATION

Once in a while one encounters an instance of aseptic necrosis developing in one or even both femoral heads for which there seems to be no reasonable explanation. In these cases, that is, the necrosis must be considered idiopathic. The patient in the case illustrated was a man 50 years of age. He was admitted to the hospital with a history of pain of 6 months' duration, referable to the left hip area. The pain was aggravated by walking and eased by bed rest when the leg was held in flexion. Though the pain was not very disabling at first, it had become increasingly so during the few months preceding admission to the hospital. During this time, too, the patient walked with a limp.

The general physical examination revealed nothing remarkable. Roentgenographic examination of the affected hip area showed that the femoral head was deformed, being flattened and mushroomed. The joint space was narrowed and the head protruded somewhat out of the acetabulum. Furthermore, the x-ray picture showed large irregular areas of radiopacity in the head, interspersed with other areas that were relatively radiolucent. On the basis of the x-ray findings and the clinical history, it was concluded that this was a case of aseptic necrosis of the femoral head in which the etiology was obscure (Fig. 6).

Pathologic Changes in the Femoral Head.—The head in question was received in several pieces. When reconstructed it showed that the articular cartilage was, for the most part, lusterless and that in some places the cartilage was loosened from the underlying bone. In other places the cartilage was absent from the bone surface. Sectioning of the several pieces of the femoral head which were received showed a good deal of yellowish discoloration of the osseous substance, representing necrotic bone the intertrabecular marrow spaces of which were apparently filled with granular detritus. Histologic examination confirmed the gross findings. Much of the osseous tissue of the femoral head was nonviable. The intertrabecular fatty marrow was also nonviable, and in many places the

FIG. 6

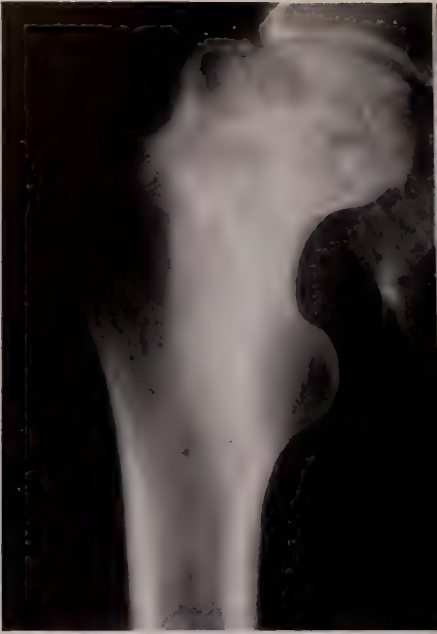


FIG. 7



FIG. 8

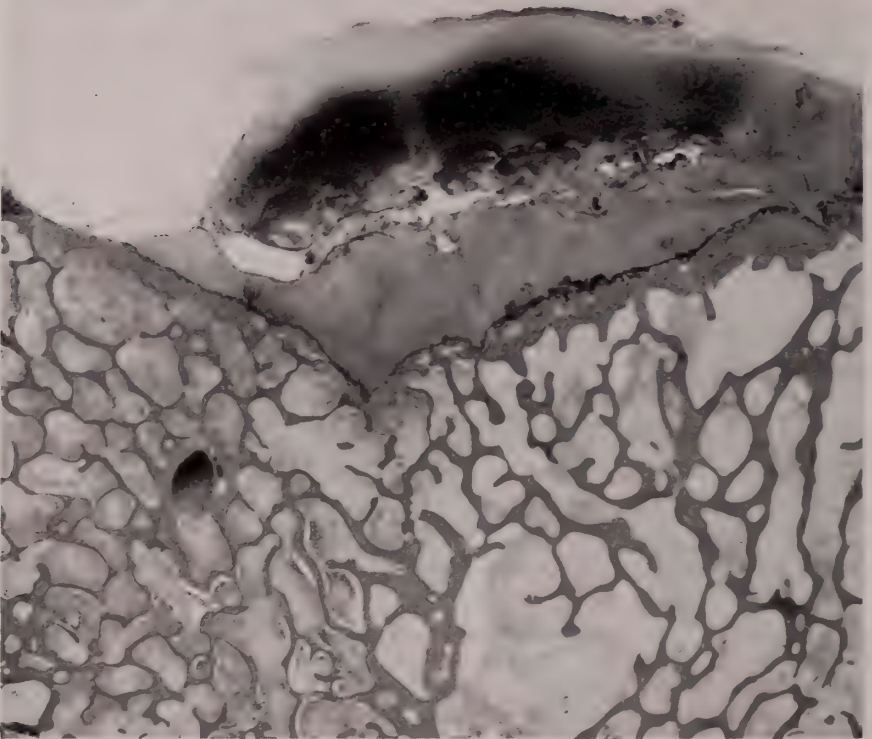


FIG. 6. Roentgenograph of a deformed and substantially necrotic femoral head in the case of a man 50 years of age who had pain and disability, of 6 months' standing, referable to the hip. The underlying cause for the necrosis was never clarified.

FIG. 7. Roentgenograph showing a necrotic, mushroomed and otherwise deformed femoral head in the case of a child 9 years of age who was suffering from Gaucher's disease.

FIG. 8. Photomicrograph ($\times 4$) showing the articular end of a femoral head from a case of Gaucher's disease. To the left the intertrabecular marrow spaces showed, on higher magnification, compacted masses of Gaucher cells. To the right the Gaucher cells in the intertrabecular marrow spaces have undergone necrosis and the osseous tissue is nonviable. Above, note the osteochondral fracture fragment. Immediately beneath the articular cartilage, the osseous tissue was necrotic, as were the Gaucher cells in the intertrabecular marrow spaces.

intertrabecular marrow spaces contained a considerable amount of granular calcific detritus.

ASEPTIC NECROSIS IN GAUCHER'S DISEASE

The fact that bones are implicated in cases of Gaucher's disease is well recognized. In some cases, though the bone marrow is heavily infiltrated with Gaucher cells, there is no roentgenographic evidence of alteration of the bones. In other cases, however, the presence of abundant Gaucher cells in the bone marrow is associated with structural alterations at least in some of the bones. In this connection it is significant that subjects of the disease who have undergone splenectomies are the ones who are most likely to present conspicuous skeletal changes. When the bones are affected, a common finding is expansion of the contours (clubbing) of the lower portions of the femora. However, what is pertinent here is the occurrence of alterations in the femoral head in Gaucher's disease. Specifically, the head occasionally undergoes aseptic necrosis and may even collapse. A necrotic and otherwise altered head in a child suffering from Gaucher's disease may simulate in its x-ray picture the changes to be noted in connection with the aseptic necrosis underlying Perthes' disease.

The following case serves to illustrate the very advanced changes sometimes to be observed in the femoral head in children affected with Gaucher's disease. The patient was a child 9 years of age who had undergone a splenectomy for Gaucher's disease at another institution about a year before he was admitted here. About 6 months prior to admission he developed a left-sided limp and began to have occasional pain referred to the knee. Clinical examination showed that there was some limitation of internal rotation and severe limitation of abduction.

Roentgenographic examination of the affected femoral head showed that it was flattened and mushroomed onto the neck (Fig. 7). A narrow zone of the head, immediately beneath the cartilage, showed increased radiopacity at least in part. Beneath this zone the head cast a fragmented shadow. Beyond this area the neck of the bone appeared rather radiopaque, and small curlicue radiopacities extended down toward the shaft. Altogether, the x-ray findings were indistinguishable from those to be noted when the necrosis is due to other causes.

Pathologic Changes.—Tissue from the femoral head was not available in the case mentioned above. However, tissue sections were available from another case which had yielded comparable roentgenographic findings. In these sections one could note large fields in which the intertrabecular marrow spaces were crowded with Gaucher cells, and in some places large fields of these cells were necrotic. In these areas the bone trabeculae were also necrotic. In addition to these changes, the femoral head presented a superficial osteochondral fracture fragment (Fig. 8).

The changes in the femoral head in Gaucher's disease are to be related to the interference with the local blood supply. It is pertinent in this connection that, at least in the spleen and liver, collections of Gaucher cells have been found within vascular channels. However, it is not clear whether the blood supply is

interrupted through the agency of intravascular plugs of Gaucher cells or through compression of the local vessels by extravascular accumulations of these cells (3, 4, 5, 6). The histologic findings in the tissue sections of the femoral head just described did not support the conception that the interruption of the blood supply was due to intravascular blockage.

DISCUSSION

Aseptic bone necrosis—that is, death of a bone area without the agency of infection—is a subject which has long intrigued pathologists, roentgenologists, and surgeons. The aseptic necrosis considered in most of the earlier studies was that underlying so-called osteochondritis dissecans of the lower end of the femur, that of Legg-Perthes' disease of the capital femoral epiphysis, and that represented by such other localized necroses as Kienböck's disease of the carpal semilunar and Freiberg's disease of the head of the second metacarpal bone.

That the affected bone part in such cases had suffered from local interruption of its blood supply was understood from the start. The question was how to account for this interruption in such cases, and this question is still not fully answered. In his attempt at an explanation, Axhausen (7) introduced the concept of bacterial embolization ending in "bland" infarction of the part. Specifically, his idea was that clumps of bacteria of one type or another reached the affected bone area and blocked some of its crucial vessels, but that, since the bacteria had died off without having produced a local infection, the thrombosis results in a non-infected bland infarct. However, neither Axhausen nor anyone else has ever observed such emboli, for instance, in a femoral head affected with Legg-Perthes' disease, or in relation to a focus of osteochondritis dissecans at the condylar end of a femur. Also, the idea that the necrosis in such cases ensues from local obliterating endarteritis can safely be rejected.

Whatever the fundamental cause may be, we know that the necrosis does not develop through the mediation of a fracture of the part. This does not mean that trauma may not play an etiologic role. However, the trauma (if any is demonstrable) is more likely to consist of exaggerated functional punishment to the part than of a single acute blow. Even if we accept the role of trauma (functional or acute), it is difficult to explain just how this acts to bring about the condition. In this connection some (8) have maintained that acute trauma or trauma from abnormal functioning may injure the vessels supplying the part and hence lead to aseptic bone necrosis, but this conception, too, is hypothetical.

In contrast to the instances of localized aseptic bone necrosis just discussed, in which the cause of the interruption of the local blood supply is difficult to evaluate, the cases discussed in the body of this article are mainly cases in which the underlying local interruption of circulation could be explained. Once the aseptic necrosis of the femoral head has established itself, complications due to secondary changes may follow. These include the delimitation of smaller or larger osteochondral fracture fragments, detachment of fragments of cartilage and or cartilage and bone which may enter the joint as loose bodies, and subsequently the development of osteoarthritic changes in the affected hip joint in

consequence of malalignment of the articular surfaces associated with functional trauma. Indeed, the aseptic necrosis, once established, favors collapse of the femoral head and alteration of its articular cartilage, reinforcing the vicious cycle of malalignment and functional trauma.

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OCULAR MANIFESTATIONS OF COLLAGEN DISEASES

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Klemperer, Pollack and Baehr (1) in 1942 proposed the term collagen diseases "to call the attention of medical investigators to a group of diseases which are characterized by systemic involvement of the connective tissue, specifically of its inter-cellular components", and they closed their paper "with the hope that physics and chemistry would investigate the collagenous tissues as a colloidal system."

Meyer (2) investigated the role of hyaluronic acid and realized that this muco-polysaccharide accumulated within the connective tissue as a result of which the chemical analysis of the structure of the ground substance was begun. Recently, it has been concluded that the anatomic site of the connective tissue alteration is the ground substance where there is swelling with increased thickening of the collagen fibers. The fibrinoid deposits which occur are a result of a precipitation of muco-polysaccharides by the action of a basic protein. According to Klemperer (1), "the morphologic key manifestations in this group of diseases collectively called collagen diseases is the fibrinoid alteration of the connective tissue. It occurs in wide distribution and strikingly in the small vessels of the body as shown by Sokoloff in his cases of scleroderma." The nature of fibrinoid is the main problem in the anatomic pathology of collagen diseases and it is important to remember that in systemic lupus erythematosus there is evidence that fibrinoid contains degradation products of desoxyribonucleic acid. Recently, an abnormality of the blood plasma protein has been observed in the collagen diseases which is so striking that Ehrlich has suggested the term dysgamma-globulinemias instead of collagen diseases. Klemperer (1) stresses the view that there seems to be a relationship between blood plasma proteins and the ground substance of the connective tissues.

Maumenee (3) thinks that the term "systemic diseases of the connective tissue" is a more appropriate designation than collagen diseases. Klemperer (1) has shown that fibrinoid degeneration occurs in many conditions such as peptic ulcers, pancreatic necrosis, acute bacterial infections, repeated injections of epinephrin or even simple squeezing of the skin of a rat. He states that just because one of these conditions is caused by an allergic response it does not necessarily follow that a similar etiology will be found in the other diseases.

The systemic diseases included under the term collagen diseases are lupus erythematosus disseminatus, periarteritis nodosa, dermatomyositis, generalized scleroderma, serum sickness, rheumatic fever and rheumatoid arthritis.

Retinal, optic nerve and uveal involvement are the most constant findings in lupus erythematosus disseminatus, periarteritis nodosa, dermatomyositis and serum sickness. These findings consist of small, round or oval cotton-wool exudates or cytoid bodies and flame-shaped hemorrhages in the nerve fiber layer of the retina, edema of the nerve head and transudates and leukocytic cell infiltra-

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tion in the choroid. The exact nature of the cytoid bodies or cotton-wool exudates is not known, but they probably represent either swollen, degenerating neuroglia fibers or transudates. Friedenwald (4) believed they are minute ischemic infarcts. They are similar in appearance to the cotton wool exudates seen in hypertensive retinitis but are never larger than the disc and have been confused with metastatic tubercles. In the absence of hypertension or diabetes the finding of cytoid bodies is suggestive of lupus. In the early stages of rheumatic fever, rheumatoid arthritis and disseminated lupus erythematosus the differential diagnosis is sometimes difficult. It has been pointed out, however, that the presence of fundus changes differentiates lupus erythematosus from the other two conditions because in rheumatic fever and rheumatoid arthritis fundus changes do not occur.

Iritis occasionally occurs in periarteritis nodosa and dermatomyositis. Ophthalmoscopic changes of the choroid in patients suffering from periarteritis nodosa appear first as greyish blurred lesions as shown by Goldstein and Wexler (5). Pathologic changes characteristic for periarteritis nodosa have been found in the vessels of the iris and ciliary body and yet no clinical symptoms have been observed in these eyes. In the overwhelming majority of cases where periarteritis nodosa is complicated by a retinal detachment the latter is caused by a choroidal periarteritis nodosa. However, cases do seem to occur where this retinal detachment is a consequence of the albuminuric retinitis which is present in periarteritis nodosa. Friedenwald and Rones (4) and Boeck (6) were able to prove conclusively on the basis of anatomic examinations that the albuminuric retinitis in periarteritis nodosa does not constitute a manifestation of ocular periarteritis nodosa. The albuminuric retinitis is rather a sign of the serious effects of the general disease on the kidney and the circulation. Retinal perivasculitis and occlusion of the central retinal artery have also been seen in periarteritis nodosa. Episcleritis and nodular scleritis are frequent complications in periarteritis nodosa, rheumatoid arthritis and dermatomyositis. Sclero-malacia perforans and marginal Mooren's-like ulcers of the cornea have been noted in periarteritis nodosa and in rheumatic fever. The incidence of iritis in rheumatoid involvement of the spine is much more frequent than in adult peripheral arthritis.

The other eye lesions in the collagen diseases are rare. The lids may be involved in the skin changes of lupus erythematosus disseminatus and scleroderma, sometimes producing an ectropion. Lid, conjunctival and orbital edema may occur. In dermatomyositis, there may occur edema of the lids with a reddish blue-brown hue, so-called heliotrope eyelids. Cataracts are complications of scleroderma and serum sickness. Ocular palsies, nystagmus and transient blindness may be present in lupus erythematosus disseminatus, periarteritis nodosa and serum sickness as a result of central nervous system involvement. Band-shaped corneal opacity, iridocyclitis and cataract occur in Still's disease.

Conditions possibly related to collagen diseases are:

A. Temporal arteritis which may be related to, if not a form of periarteritis nodosa.

B. Reiter's syndrome which consists of conjunctivitis, urethritis, arthritis and occasionally iritis.

C. Steven's-Johnson's Disease or generalized cutaneous eruptions, stomatitis and conjunctivitis.

D. Behcet's Syndrome with recurrent hypopion iritis, stomal and genital ulcers and at times thrombo-phlebitis, erythema nodosa pyoderma and arthritis.

E. Kerato-conjunctivitis sicca has been tentatively included.

F. Buerger's disease, in which thromboangitis of the retinal, iris and ciliary vessels occurs not infrequently.

A resume of the ocular manifestations of collagen diseases would include:

- (a) Lids—erythema and edema.
- (b) Conjunctiva—phlyctenules, hyperemia, edema.
- (c) Cornea—sclerosing keratitis.
- (d) Sclera—episcleritis, nodular and brawny scleritis, sclero-malacia perforans.
- (e) Uvea—uveitis, choroidal infarcts.
- (f) Retina—hemorrhage, either petechial or superficial; exudates, such as cytoid bodies.
- (g) Vascular—such as periphlebitis, periarteritis and occlusions.
- (h) Visual fields—vascular lesions, optic pathways.
- (i) Disfunction of pupil and extra-ocular muscle palsies—from vascular lesions in the central nervous system.
- (j) Optic nerve—neuritis.

SPECIFIC THERAPY

To institute specific therapy in the presence of collagen diseases, it is advisable to perform meticulous clinical, radiographic and endoscopic studies for detection of early operable malignancy. There should be removal of all possible allergens whether bacterial, viral or drugs and desensitization when hypersensitivity is demonstrated.

Daraprim® in a dose of 25 mg. per week, then raised in two steps to 25 mg. daily produced only slight improvement in the few individuals in whom it was tried so far.

Steroid therapy in the form of A.C.T.H. and/or metacorten is usually quite helpful.

LOCAL THERAPY

Anti-inflammatory agents such as steroids and cycloplegics to put the ciliary body at rest are always beneficial.

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QUANTITATIVE CYTOCHEMISTRY (MICROSPECTROPHOTOMETRY), A FRUITFUL APPROACH TO THE STUDY OF DISEASE*

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Cytochemistry, the field which deals with the chemical composition of cells has interested workers in the biological and medical fields for a long time. Ever since the microscope was discovered and staining methods developed which allowed the study of the morphology of cells, questions as to the *chemical* components of cells and their behavior under different conditions have been raised by the cytologist, histologist and pathologist. But it was actually the biochemist and not the microscopist who has given us the foundation of our present knowledge of the chemical nature of cells.

At the end of the last century, two brilliant biochemists, Miescher (1) and Kossel (2), demonstrated for the first time that the essential building stones of all cells of animals, plants and bacteria are the nucleoproteins, a salt-like compound of nucleic acids and proteins. Their fundamental discovery and the subsequent contributions by other biochemists stimulated the student of cell research to relate the biochemical findings to the observations which he made under the microscope. Which structures of the cells contained the nucleoproteins and how could these compounds be demonstrated *in situ* in the cells or cell parts such as the cytoplasm, nucleus, nucleolus or chromosomes? These were pertinent questions because, in spite of the great contributions resulting from the biochemical studies, such analyses were unable to answer the more specific questions just mentioned. This is mainly due to the fact that the biochemical analysis can be made only after the tissues are macerated and the cells destroyed in order to extract the substances to be investigated. The development of staining procedures for cells and especially the early effort to interpret the staining of cellular structures in chemical terms reflect the endeavor of microscopists to correlate *structure of cells with chemical constituents*. While the use of stains was more or less empirical, this approach actually started an era of what might be called cytochemical research (3, 4, 5).

The chemical makeup of tissues and cells should be, and is, of particular interest to the pathologist who is confronted with the task of studying and diagnosing disease on the basis of morphological alterations of tissue elements. Although microscopic examinations of tissues have yielded a wealth of information on etiology and pathogenesis of disease, many pathologists have become aware of the limitations imposed by such purely structural studies and have recognized

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the importance of the chemical study of tissues. After all, in the final analysis, a change in the morphological appearance of a tissue element is the expression of alterations in the chemical constituents which make up that structure. Since the cell occupies a fundamental position in tissues and is probably one of the primary targets hit by the injurious agent, study of the *chemical constituents* of the cell would obviously offer important information.

The investigation of disease at the cytochemical level has greatly profited by the application of a special technique called microspectrophotometry or cytophotometry. We owe to Caspersson's ingenious pioneering in 1936 (6) the development of this new type of microscopy. By combining the microscope with a photometric device, Caspersson showed that it was possible to use the microscope as a tool not only for morphological but also for chemical analysis of cells. The analyses can be done in situ in microscopic sections of fixed tissues on single cells or cell parts so that, without destroying either the architecture of the cells or their relationship within a tissue, a comparison of cell morphology with its chemical composition can be made.

The basic principle of microspectrophotometry is actually very simple. As in photometric chemical analysis of solutions, the amount of light absorbed at specific wavelengths by a cell structure is used as a basis for the qualitative and quantitative analysis of the intracellular substances. Thus microspectrophotometry closely resembles analytical chemistry, but has the advantage of directly correlating the microscopic appearance of a cell structure with its chemical makeup.

Since the nucleic acids and proteins represent important chemical components of cells and are easily retained in fixed tissues, they are especially suited to analysis by microspectrophotometry. There are at the present time, two main microspectrophotometric methods for determining nucleic acids and proteins in microscopic preparations, a direct one and an indirect one. The direct method, developed by Caspersson and his school (6, 7) utilizes, in unstained preparations, the natural absorption of nucleic acids and proteins in ultraviolet light at a wavelength characteristic for these substances. The indirect method, described by Pollister and Ris in 1947 (8) first applies a staining reaction specific for nucleic acids and proteins to the preparations, and then utilizes the light absorption of the stained structures at wavelengths characteristic for these dyes (9).

The application of microspectrophotometry to the study of pathological processes has been of special interest to the cytochemical laboratory which was initiated seven years ago by Dr. Alan R. Moritz, Director of the Institute of Pathology, Western Reserve University. It was felt that the unique opportunity afforded by microspectrophotometry for carrying out simultaneous chemical and morphological analyses on the same cell structure might advance our knowledge of etiology and pathogenesis of disease. Furthermore, it was hoped that the early diagnosis of disease would be greatly aided because it was found that microspectrophotometry also offers the possibility of detecting changes in intracellular substances before structural alterations in cells manifest themselves under the microscope (10).

One of the intracellular substances on which our attention has been especially focused is desoxyribose nucleic acid (DNA). DNA is present in the nuclei of all cells, is an essential constituent of chromosomes, is closely correlated with chromosomal status (11) and is possibly an integral part of the genetic material. In the last ten years, due to the discovery of Boivin, Vendrely and Vendrely (12), it has also been shown that in normal cells of all tissues, irrespective of their physiologic function, the DNA content is remarkably constant and the amount in the diploid somatic cell is twice that found in the haploid sperm of the same species. In view of the important role of DNA under normal conditions for cell life and cell continuity, its quantitative stability and its close relationship to the genes, the study of DNA in abnormal cells and in cells under pathological conditions is obviously of great interest and promises a fruitful approach to the elucidation of disease. We have explored the behavior of DNA in a variety of pathological conditions by Feulgen microspectrophotometry. The specificity and validity of this method for quantitative determinations of DNA have been fully established (9, 13, 14, 15). Some of the investigations which we carried out along these lines will be briefly reviewed in the following.

One of the first problems with which we were concerned was the study of DNA in the malignant transformation of cells in human tissues (10). A priori, it was reasonable to expect that the DNA content of tumor cells would be different from that in normal cells. This concept was suggested by the increase in size and staining density so frequently observed by the pathologists in tumors. Since very little was known about the DNA content of cells in normal human tissues prior to this study, a comparative extensive study on the DNA content of a variety of normal and malignant human tissues had to be carried out to establish a baseline. DNA measurements were made of nearly 3000 individual cells from 49 normal and 27 malignant tissues. It was found that all the normal tissues no matter what their origin or metabolic function, contained cells with a similar basic mean DNA content, a finding which was in accordance with the original observations in animal tissues (12). This DNA content (2.8 arbitrary units or 5.6×10^{-9} mgm) was approximately twice that found in the sperm cells and is characteristic for human cells with a diploid chromosomal complement. Some adult tissues such as liver, also carry cells with nearly exact multiple amounts of the diploid cells, indicating correlation of the DNA content with the presence of multiple chromosomal complements, that is polyploidy or polyteny.

In contrast to this constant and orderly pattern of DNA in normal tissues, the DNA content of precancerous lesions and malignant tumors was found to be considerably higher and revealed a much larger scatter from cell to cell. An example for a precancerous lesion is given in Figure 1 and an example for a malignant tumor is given in Figure 2. Figure 1 shows how the DNA values spread in senile keratosis (Fig. 1B) in contrast to the narrow range prevailing both in a normal skin (Fig. 1A) and in a skin exhibiting inflammation from a case of psoriasis (Fig. 1C). Figure 2 shows the difference in DNA behavior between a primary adenocarcinoma of the stomach (Fig. 2A), a metastasis from this tumor to a lymph node (Fig. 2D) and the surrounding normal portions of stomach (Fig.

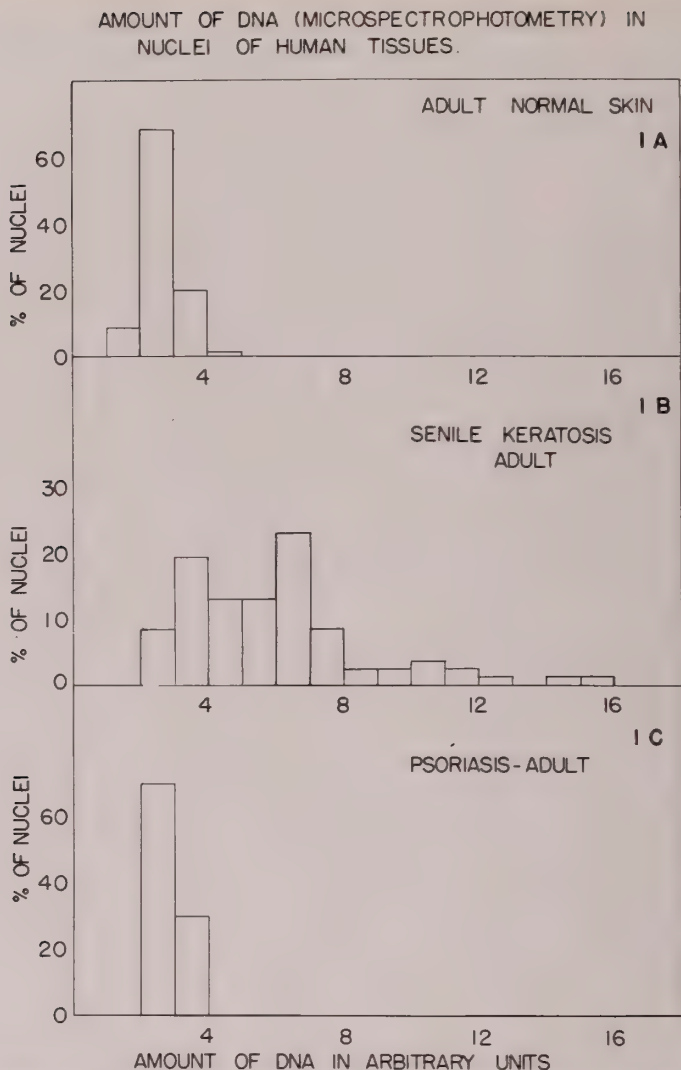


FIG. 1. Amount of DNA in skin nuclei. (A) Increase and spread of values in the precancerous lesion, senile keratosis (cf. Fig. 1C). (B) Preponderant diploid amount and narrow range in adjacent normal skin. (C) Preponderant diploid amount and narrow range in a case of psoriasis.

2B) and lymph node (Fig. 2C). Here again, the DNA values in the normal stomach and lymph node agree with the values for the normal skin, while the tumors show a greater amount of DNA and larger scatter. Thus the DNA findings in tumors are indeed in accordance with the morphology of tumor cells exhibiting increase in size and staining intensity. However, since increase in DNA is also found in cells of rapidly growing normal tissues undergoing mitosis such as embryonic tissues, the deviating DNA values in malignant tissues are probably due to the mitotic processes in tumors and cannot be considered a specific criterion for diagnosing malignancy per se. On the other hand, it must be kept in

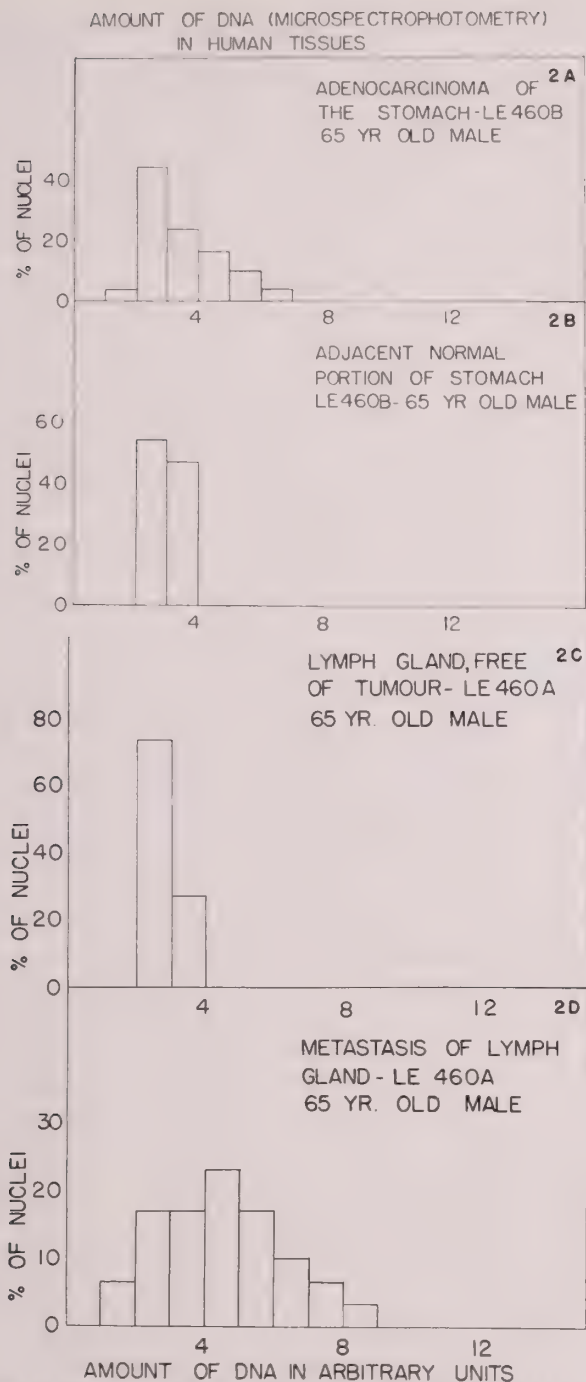


FIG. 2. Amount of DNA in a tumor and in a metastatic nodule. (A) Increase and spread of values in adenocarcinoma of the stomach (mucosal nuclei). (B) Preponderant diploid amount and narrow range in adjacent normal mucosa. (C) Preponderant diploid amount and narrow range in normal parenchyma of a lymph node from the same case. (D) Increase and spread of values in a metastatic nodule in this lymph node.

mind that *normal* adult tissues do not usually undergo mitosis and consequently exhibit the constant basic amount of DNA in their cells as shown for normal skin, stomach and lymph node in Figures 1 and 2.

Therefore, an increase in DNA values in cells of an adult tissue should evoke suspicion of neoplastic growth unless regeneration is to be expected. One may argue of course, that microscopic examination of a tissue for mitosis is much simpler and will lead to the same results. However, the absence of mitotic figures in a tissue does not exclude the possibility that mitosis is taking place. If the time period of the mitotic cycle is very rapid, mitotic figures may be missed completely. Since DNA synthesis occurs at a very early stage of the mitotic process, namely already in interphase (16, 17), and is thus independent of the time period of the mitotic cycle, DNA increase can be used as a most sensitive indicator for a division process. Studies of this kind may be particularly helpful in the cases which the pathologist designates as borderline cases, such as carcinoma in situ, some cases of low-grade malignancy, and in brief, cases in which mitotic figures are scanty or absent. Although these studies clearly reveal that the malignant process has no *specific* effect on the DNA content of a nucleus, nevertheless, deviating DNA values in cells which seem morphologically normal may indicate a preparation for abnormal growth and may therefore be of help in diagnosing early malignancy.

Another abnormality in which DNA studies by Feulgen microspectrophotometry have proved to be of special diagnostic value concerns the problem of male infertility. In contrast to the remarkably constant and uniform haploid DNA content found in the spermatozoa of fertile males, the DNA content in the spermatozoa from infertile males is variable and significantly lower than that from the fertile ones (18, 19). Figure 3 is a characteristic example of the difference in DNA content between fertile and infertile men. It is evident that the DNA values from the fertile men show a very narrow range while among the infertile men, most of the values are significantly lower and show a wider scatter of the values. This finding is of special significance since the morphological appearance and size of the spermatozoa containing the normal and deficient amounts of DNA are identical. Figure 4 demonstrates the agreement in nuclear sizes of spermatozoa with normal and deficient DNA contents from fertile and infertile males respectively. The overlapping of the two curves is readily apparent. The DNA deficiency found in the spermatozoa from infertile men can be traced back to the spermatogenic cells in the testis (20). As shown in Figure 5, the primary spermatocytes, secondary spermatocytes and spermatids, exhibit a deficient DNA content in infertile males as compared with the expected normal DNA values of 4DNA, 2DNA, and 1DNA in the fertile males. Here again, as in the spermatozoa, the deficiency of DNA can be present although the histological and cytological features of the testis and of the spermatogenic cells are normal. Thus it appears that Feulgen microspectrophotometric studies of the DNA content in spermatozoa and spermatogenic cells offer a valuable tool for the diagnosis of infertility especially in those cases where microscopic and clinical diagnoses have not revealed any abnormalities to account for the male infertility.

Another pathological process where the potentialities of DNA studies in cells

MEAN AMOUNT OF DNA IN 968 SPERMATOZOA OF 13 MALES WITH PROVEN FERTILITY (55 REPEAT SAMPLES), AND IN 1891 SPERMATOZOA OF 21 MALES WITH SUSPECTED INFERTILITY (118 REPEAT SAMPLES)

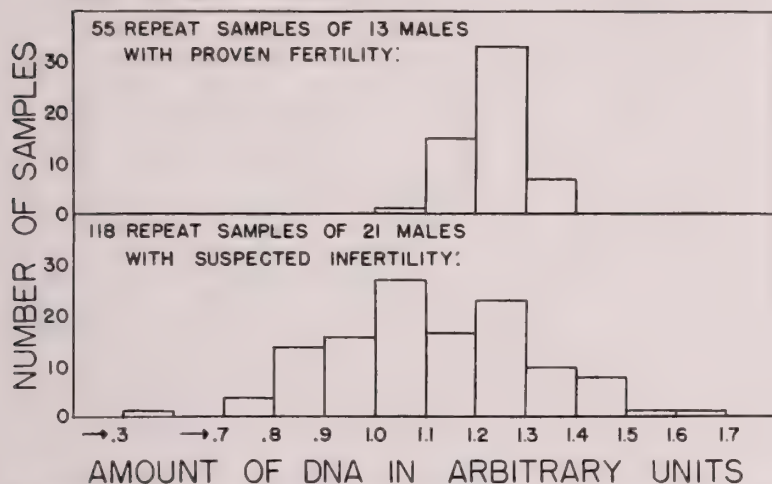


FIG. 3. *Spermatozoal nuclei*. Difference in DNA content for fertile and infertile men.

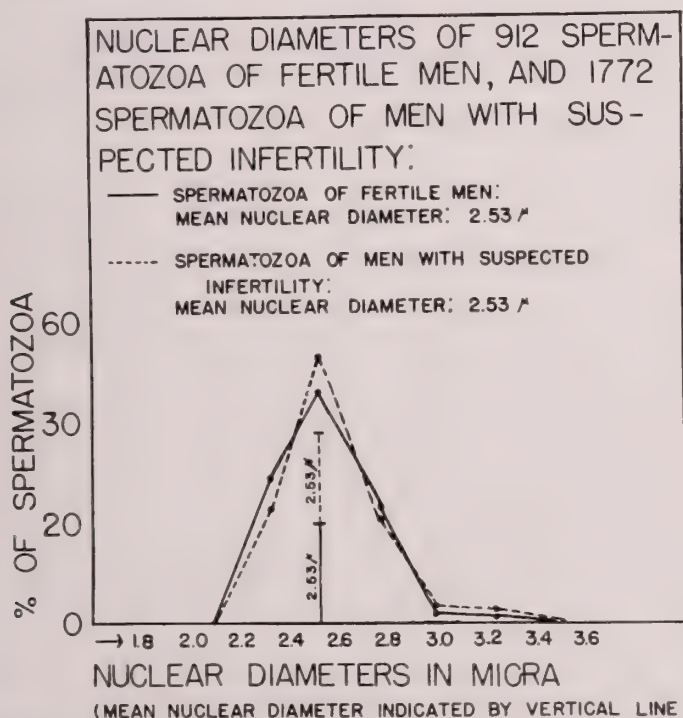


FIG. 4. *Spermatozoal nuclei*. Agreement of nuclear sizes in fertile and in infertile men.

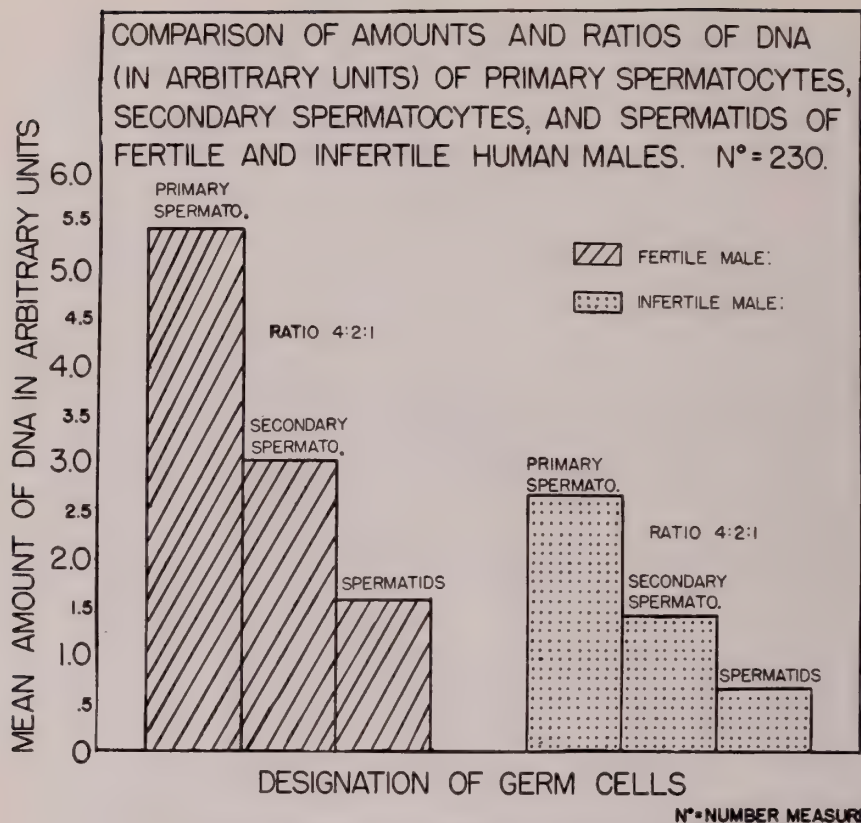
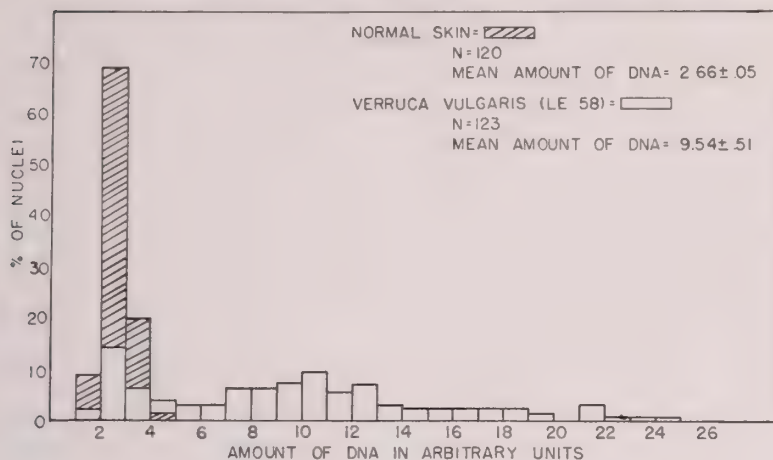


FIG. 5. *Spermatogenic nuclei*. Difference in DNA content for fertile and infertile men.

have just begun to be realized are the virus diseases. Because of the chemical composition of the viruses (many of them contain DNA) and their peculiar relationship to cells, quantitation of DNA by Feulgen microspectrophotometry may be of value for disclosing the presence of viruses in cells. In virus diseases such as molluscum contagiosum or verruca vulgaris, multiplication of the viruses within the infected cells has been demonstrated (7). If Feulgen microspectrophotometric DNA studies are done on such virus infected cells, unusually large quantities of DNA can be found in individual cells. A characteristic example is shown in Figure 6A. It is evident that the greatly increased quantity of DNA in human skin cells infected with the common wart virus, verruca vulgaris, is in marked contrast to the 2DNA content in the normal cells. These DNA values are far beyond those observed in malignant tumors and cannot be explained on the basis of mitotic processes. Associated with the greater DNA content, there is a corresponding increase in the nuclear sizes of these virus-infected cells as seen in Figure 6B.

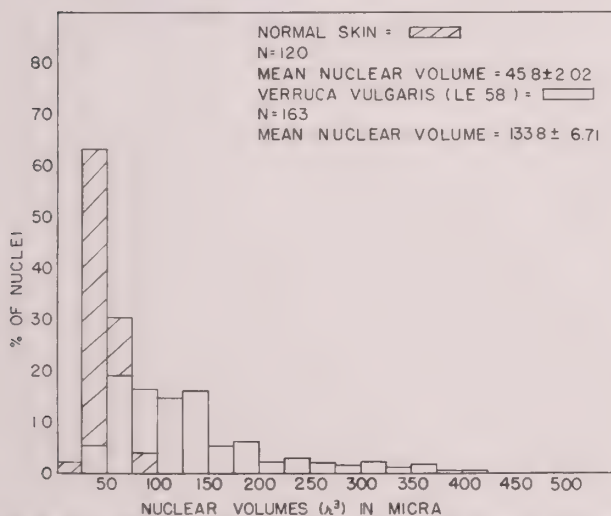
With the recognition of the importance of viruses for etiology in disease, the pathologist when confronted with a peculiar kind of abnormality in tissues, has become aware of a possible viral etiology. For example, Moritz and Leuchten-

AMOUNT OF DNA (MICROSPECTROPHOTOMETRY OF FEULGEN REACTION)
IN INDIVIDUAL NUCLEI OF HUMAN SKIN



(A)

NUCLEAR VOLUMES (μ^3) IN MICRA OF INDIVIDUAL
NUCLEI OF HUMAN SKIN



(B)

Fig. 6. Nuclei in normal skin and in the virus disease, *verruca vulgaris*. (A) Increase and spread of DNA values compared with the normal nuclei. (B) Increase and spread of nuclear sizes of the infected nuclei compared with the normal nuclei.

berger (21) observed a striking increase in the nuclear sizes (karyomegaly) of the cells from nearly all the tissues in a case of a young man who died of an unexplained respiratory disease. Feulgen microspectrophotometric studies disclosed enormous amounts of DNA in these greatly enlarged nuclei, closely resembling those found in the cells infected with *verruca vulgaris* (Figs. 6A, 6B). An example of the increase in DNA and in the nuclear sizes of the kidney nuclei from this case is given in Figures 7A and 7B respectively. It is evident that the diseased kidney

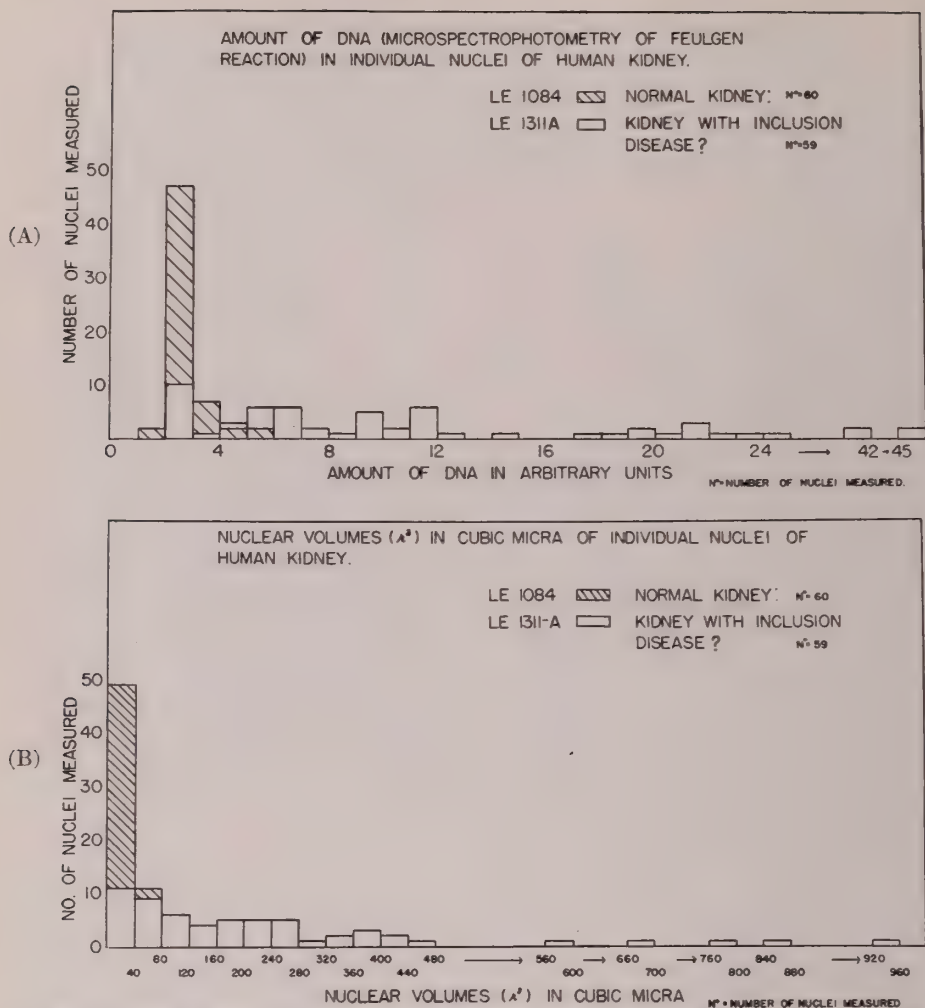


FIG. 7. Kidney nuclei in a case for which viral etiology is suggested (inclusion disease?). (A) Increase and spread of DNA values compared with normal kidney nuclei. (B) Increase and spread of nuclear sizes compared with normal kidney nuclei.

nuclei show nuclear sizes and amounts of DNA which are widely scattered and are far above those found in the normal kidney cells which have a limited size range and carry the basic diploid DNA content. Since, in addition to the DNA and nuclear size abnormalities, the configuration of the DNA masses in the nuclei of the pathological tissues was similar to that of nuclear inclusions which occur in known virus diseases or to cells experimentally infected with human viruses (22), viral infestation was suggested for this case. Although it was realized that these data were no final proof for establishing a viral origin, such a concept was offered with the hope that other pathological tissue processes of unknown etiology presenting similar findings would also be examined from a viral point of view. The features which are thought to be pathognomonic for viral

activity and which should be sought in such cases are, enormous quantities of intranuclear DNA associated with large nuclear sizes in the absence of mitosis and the presence of DNA containing inclusions in the nuclei and/or in the cytoplasm.

Perhaps this brief assessment of a few results obtained on just one of the intracellular substances will suffice to demonstrate the fruitfulness of quantitative cytochemistry (microspectrophotometry) for the study of disease. It is hoped that this presentation will stimulate microspectrophotometric investigation not only of DNA, but also of other intracellular substances such as ribose nucleic acid (RNA) (23) and proteins (24, 25, 26). This statement by no means minimizes the importance of histopathological studies, but it is felt that major advances in the elucidation of disease will come from a close integration of quantitative cytochemistry with morphology.

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THE EARLY PHASE OF ENDEMIC BANCROFTIAN FILARIASIS IN THE MALE. PATHOLOGICAL STUDY

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While the pathology of acute filarial lesions of the lymphatics in U. S. soldiers has been adequately described (1-4), little has been added to our knowledge of the pathology of endemic genital filariasis since the work of O'Connor and Hulse (5) and each observer has seen material of only a few cases (6). Meanwhile, concepts of filarial disease have been changing (7) and general knowledge of parasite-host relationships has been expanding. While studying 68 filarial lesions of the male intrascrotal organs (6) a review of the pathology of endemic filarial lesions was planned, beginning with the early phase of the infection, in order to bring the subject into line with newer concepts. Many findings confirming earlier descriptions will not be repeated here, e.g., data on distribution of worms (4, 5), degenerative changes of worms (5, 8, 9, 10), proportion of damaged and intact worms (5, 10) and of microfilariae (5) precipitates around worms and microfilariae (4, 5, 11), calcification of worms (5, 10), stages and results of granuloma formation around worms (2, 3, 4, 5, 9, 10), and differential diagnosis with other inflammatory diseases, especially tuberculosis (2, 4, 8). Confirmatory and new findings will be presented on the following aspects of the disease: (a) Early lymph vessel damage: (b) Early vein damage: (c) Early exudative inflammation: (d) Variability of the early tissue reaction.

To the previously collected cases of endemic genital filariasis (6), five new cases were added. From the 73 cases available, all confirmed by demonstration of the adult worm, 24 early cases were selected. These showed acute or subacute funiculoepididymitis or periorchitis (12) and each contained at least one intact or recently damaged worm. 23 of these were surgical specimens as follows: 6 orchiectomies, 15 fragments or segments of spermatic cord and 2 epididymectomies. One specimen was obtained at autopsy from a lethal acute funiculoepididymitis and periorchitis with bacterial infection and septicemia (13). Clinical data on these cases were scanty. Most had shown no filarial symptoms prior to the episode motivating surgery (14). Three cases were known to be recurrent. The chronological duration of the disease—as in most endemic cases—could not be adequately determined. Gross specimens were available for a few recent accessions, but were utilized for studying the location of worms by means of a clearing method (6). The histological sections, stained with Hematoxylin-Eosin, were reviewed, occasionally after restaining or special staining with the Verhoeff, Ziehl-Neelsen, or Gram-Weigert method. Step sections were available in two cases. It is hoped that the rarity and interest of the material will compensate for the deficiencies inherent in purely histopathological study.

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FIG. 1. Lymphangiectasia: Multiple cross-sections of a coiled adult worm are seen occupying the dilated and inflamed lymph vessel. The amorphous material appears granular in this section. Hematoxylin-Eosin (restained slide).

DESCRIPTION OF FINDINGS

I. *Evidence of early lymph vessel damage.* For easy classification, all lesions were systematized as follows:¹

A.—*Lymphangiectasia* (2,4) (Fig. 1). Dilation of lymph vessel containing faintly staining, usually eosinophilic material, with moderate or without parietal inflammation.

B. *Lymphangiohemorrhage* (Fig. 2). Dilated lymph vessel, similar to above, but containing unclotted blood.

C. *Parietal Lymphangitis, Polypoid* (4) (Fig. 3) or *Non-Polypoid* (Fig. 4). The lymph vessel is free of thrombosis. Its wall is infiltrated by inflammatory cells and its endothelium is prominent.

D. *Thrombolympangitis, Recent* (Fig. 5), *Organizing* (Fig. 6), or *Septic* (Fig. 7). The lymph vessel shows parietal inflammation and contains plugs of clotted blood, fibrin, inflammatory cells or a mixture of these; or it is obstructed by organizing granulation tissue. In the septic type neutrophils predominate and there is fibrin mixed with nuclear debris.

E. *Granulomatous Thrombolympangitis* (9) (Fig. 8). The lymph vessel is heavily infiltrated and inflamed, its parietal structures may be disgregated. The granulomatous tissue occupying its lumen includes multinucleated giant cells, epithelioid histocytes and swollen endothelial cells, as well as aggregates of polys or eosinophils.

¹ When detailed descriptions of a lesion have been made, the reference is given.

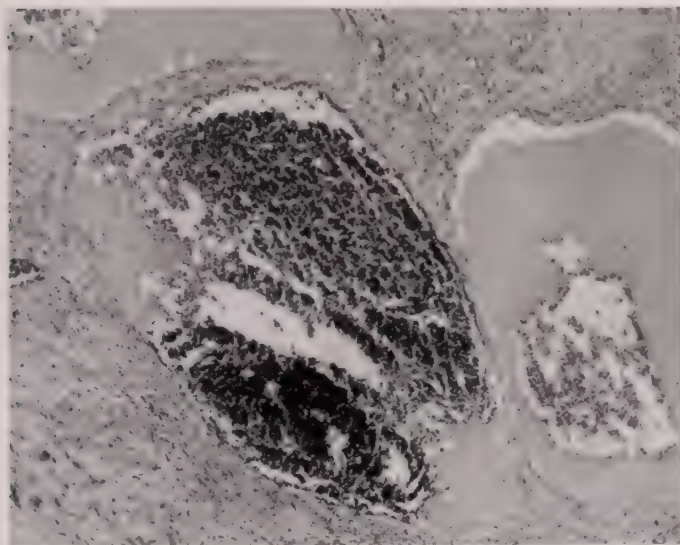


FIG. 2. Lymphangiohemorrhage: Dilated lymph channels containing unclothed blood, as well as amorphous eosinophilic material. Lymph vessel walls show inflammatory infiltration. Hematoxylin-Eosin.

The frequency of these alterations in 24 cases was as follows:

Lymphangiectasia	15
Thrombolympangitis	11
(recent only...4; recent and organizing...3; organizing only...2; septic type...2).	
Granulomatous Thrombolympangitis	10
Parietal Lymphangitis	8
(polypoid...4; non-polypoid...4).	
Lymphangiohemorrhage	6

All cases showed lymph vessel damage, but the lesions varied markedly in severity, extension and histological type. The granulomatous type of lymphangitis was most frequently seen in the vicinity of a disintegrating worm, while in more distant areas the lymph vessels showed other, less characteristic types of inflammation. Transitions from granulomatous to simple, organizing lymphangitis were observed in some sections. Eosinophilis, although frequent in the endolymphatic thrombi, were more constant around the vessels than inside.

The extension of lymphangitis was variable but due to the spatial limitation of some sections, its topography could not be fully appreciated. In general, it paralleled that of exudative inflammation (see below). Since only a few step sections were available, the relationship of the lymphangitis to the worm could not be thoroughly studied. In several instances it could be shown that lymphangitis had spread *by continuity* from a granuloma engulfing a worm. In other instances, however, no continuity could be demonstrated and lymphangitis seemed to occur in *independent foci*, or distant from the worm, e.g. in the same

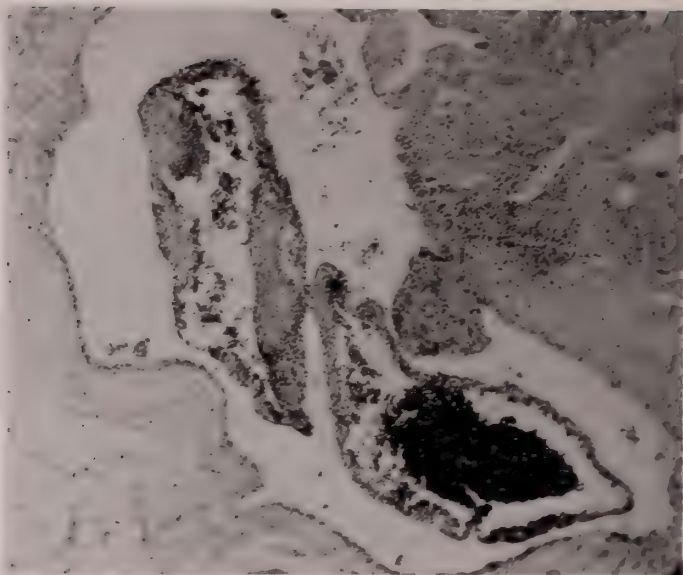


FIG. 3. Parietal lymphangitis, polypoid type: The projecting polypoid villi and the parietal infiltrate contain abundant eosinophils. Note dilation of vessel and absence of thrombosis. Hematoxylin-Eosin.



FIG. 4. Parietal lymphangitis, non-polypoid: The lymph vessel is somewhat dilated, its wall is infiltrated by inflammatory cells. It shows moderate muscular hypertrophy. An adjacent smaller lymph vessel (lower left) shows similar changes. Hematoxylin-Eosin.

cross-section but removed from the worm-containing vessels, or in the epididymis when the worm was seen in the cord.

II. *Evidence of early vein damage.* Since alterations of the veins of the cord and epididymis occur independently of filariasis, a complete description of the

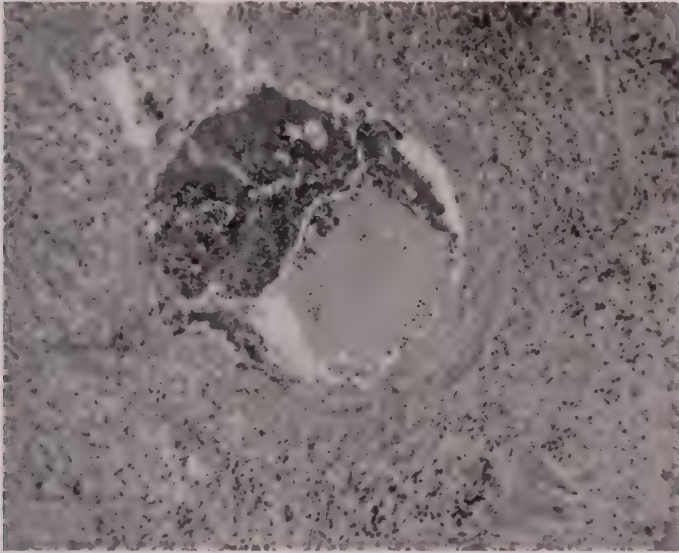


FIG. 5. Thrombolympfangitis, recent type: Part of the lumen of the lymph vessel is occupied by fibrin and red cells, the remainder shows amorphous pale staining material. There is parietal inflammation and some muscular hypertrophy. Many of the inflammatory cells are eosinophils. Hematoxylin-Eosin.

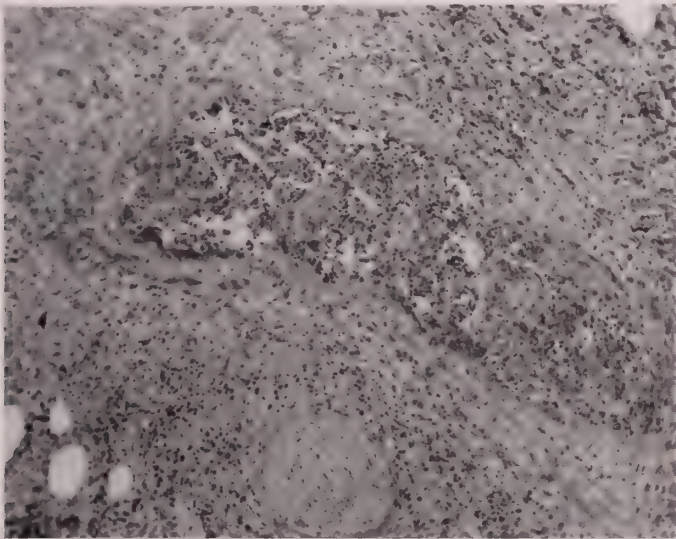


FIG. 6. Thrombolympfangitis, organizing type: The thrombus contains macrophages and fibroblasts, as well as lymphoid cells. There is endothelial swelling and proliferation. Exudative inflammation is observed in the surrounding tissues. A nerve fiber is included in the section (lower center). Hematoxylin-Eosin.

vein lesions found would serve no useful purpose. Simple congestion, varicocele, and phlebosclerosis were frequently seen. The following alterations were systematically evaluated:

A. *Parietal Phlebitis* (Fig. 9). The wall of the vein is infiltrated, with inflam-

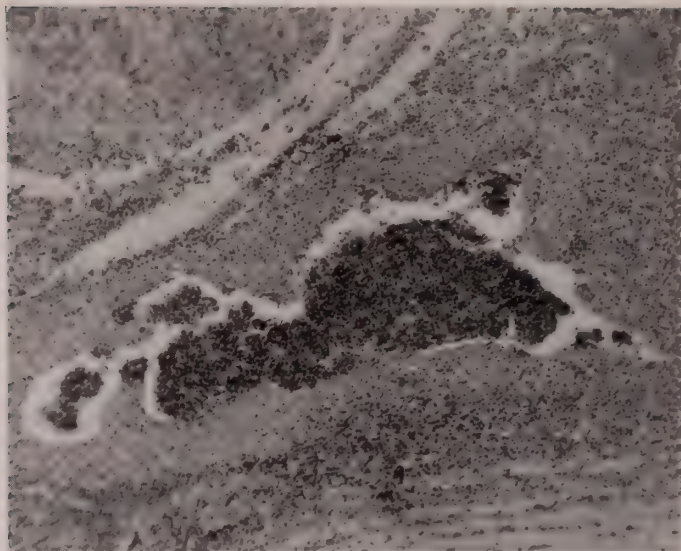


FIG. 7. Thrombolympangitis, septic type: Massed neutrophils, partially disintegrated, occupy the lymph vessel lumen. The surrounding tissue is densely infiltrated by the same cells. Hematoxylin-Eosin.

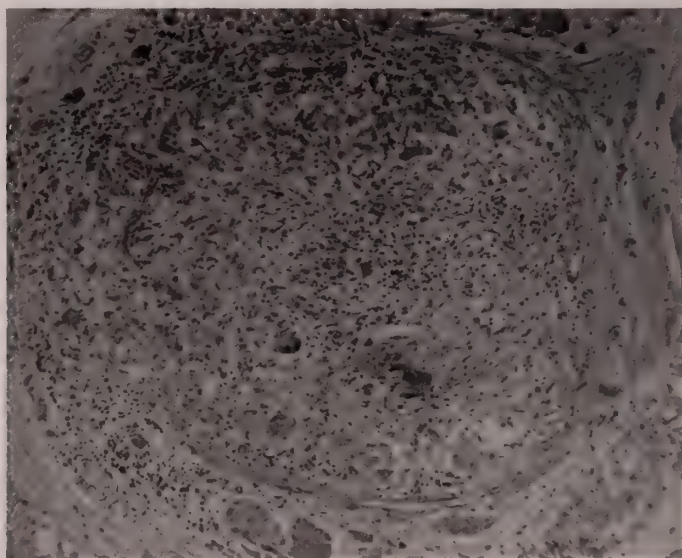


FIG. 8. Granulomatous thrombolympangitis: The parietal structures of the lymph vessel are disgregated, its lumen is occupied by epithelioid and giant cells, mixed with lymphoid cells. Capillaries are seen between the inflammatory cells. Hematoxylin-Eosin.

matory cells, the intima may be thickened, the endothelium swollen. There is no thrombosis.

B. *Thrombophlebitis, Recent* (Fig. 10) or *Organizing* (Fig. 11). The frequency of these lesions in 24 cases was the following:

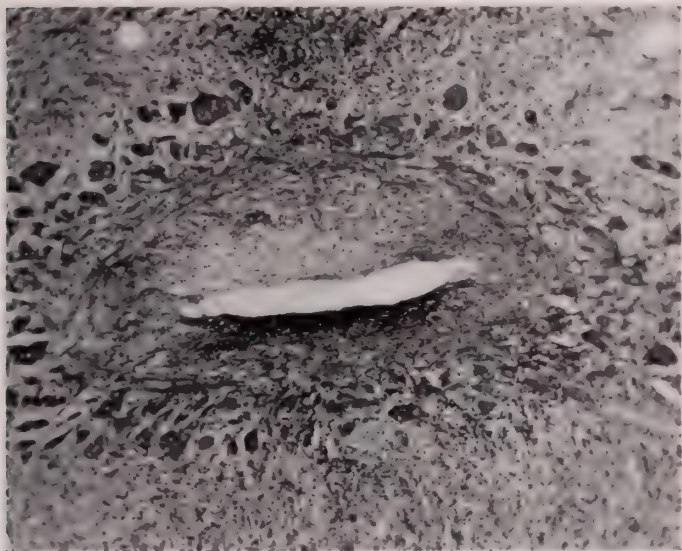


FIG. 9. Parietal phlebitis: A typically thick walled vein of the cord situated in a zone with marked exudative inflammation, shows its wall infiltrated with inflammatory cells and its intima irregularly thickened. Note absence of thrombosis. Hematoxylin-Eosin.

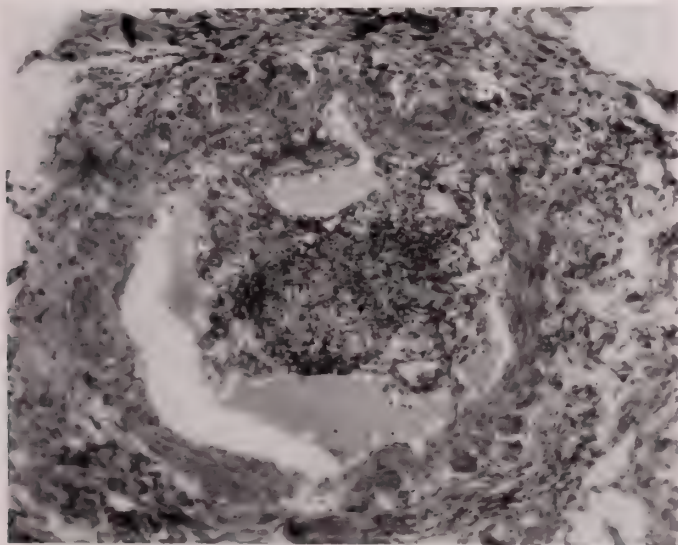


FIG. 10. Thrombophlebitis, recent type: Spermatic cord vein showing agglutinated cells and fibrin, inflammatory infiltration of wall. Hematoxylin-Eosin.

Parietal Phlebitis.....	6
Thrombophlebitis.....	9
(recent only....2; recent and organized....3; organized only....4).	

Although thrombophlebitis was found in over one-third of the cases, vein lesions were far less constant than lymph vessel lesions. In view of the difficulty of distinguishing large, inflamed lymph vessels from veins, only structures with a prominent internal elastic membrane, thick and well layered muscular wall and

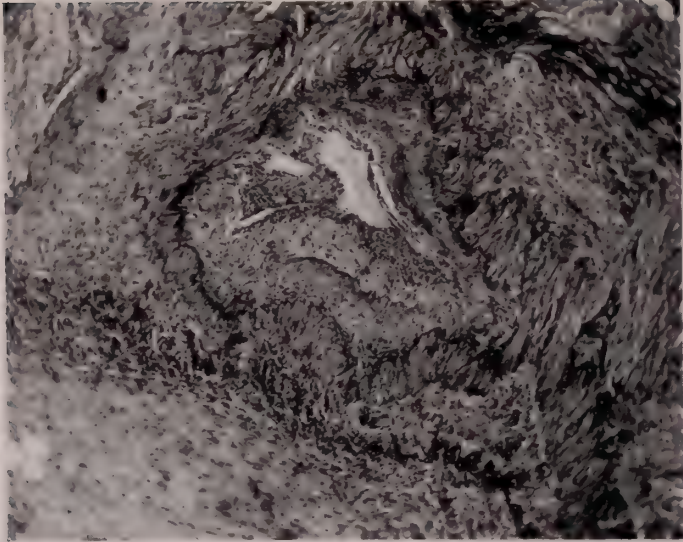


Fig. 11. Thrombophlebitis, organizing type: Thick-walled vein of cord, close to site of worm destruction. The vessel shows intimal swelling, newly formed elastic tissue and its lumen is occupied by inflammatory cells. There is initial recanalization. Verhoff's elastica stain.

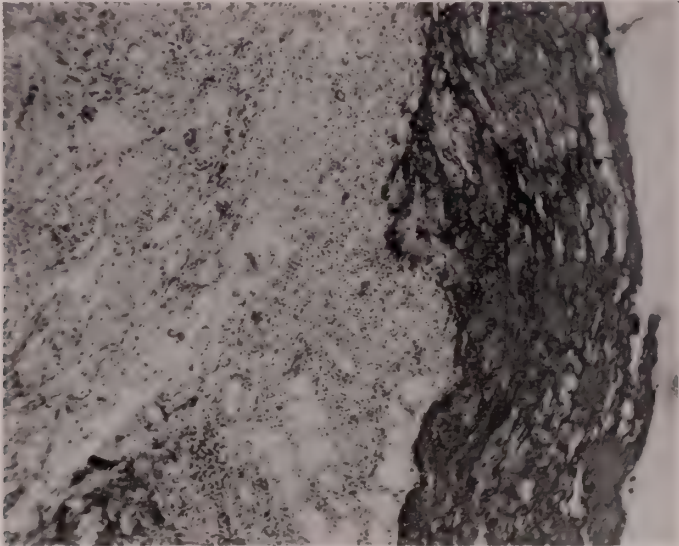


FIG. 12. Fibrinous vaginalitis, acute, of spermatic cord: The serosa is covered by a thickly layered fibrin deposit. The lax tissue shows intensive exudative inflammation. An interstitial fibrin deposit is seen in the lower left hand corner. Hematoxylin-Eosin.

containing red cells were used for the above estimations. Phlebitis was found both near and distant from filarial worms, and all vein lesions were histologically non-specific.

III. *Evidence of early exudative inflammation:* Once attention was focused away from the worm and its granuloma, it became evident that exudative inflamma-

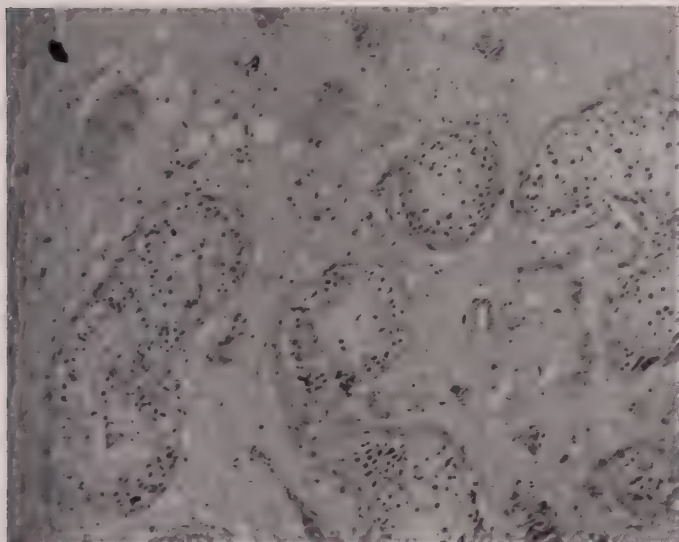


FIG. 13. Acute edematous orchitis, general view: Albuginea on left side. The tubules are separated by wide bands of edematous interstitial tissue with few inflammatory cells in exudate. Hematoxylin-Eosin.

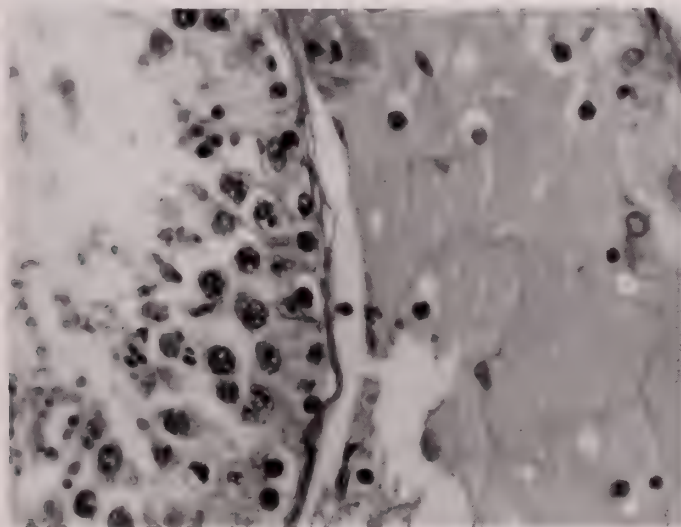


FIG. 14. Acute edematous orchitis; higher power: Shows edematous, cell-poor exudate on right, largely intact tubular structure on left. Hematoxylin-Eosin.

tion was constantly present in early filarial lesions, varying only in severity, extension and composition of the exudate. In a total of 24 cases, exudative inflammation was

A. Marked and widespread in	13 cases
B. Moderate and localized in	9 cases
C. Mild in	2 cases

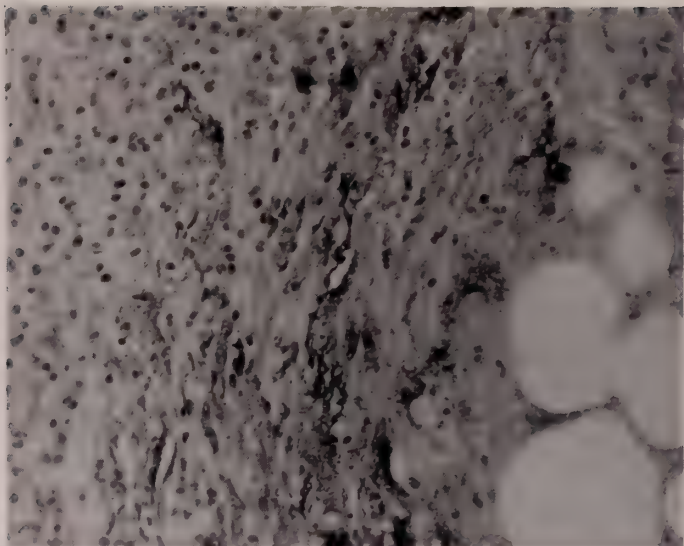


FIG. 15. Exudative inflammation, fibrin deposition: Strands of fibrin in the intensively inflamed interstitial tissue of the spermatic cord. Gram Weigert fibrin stain.

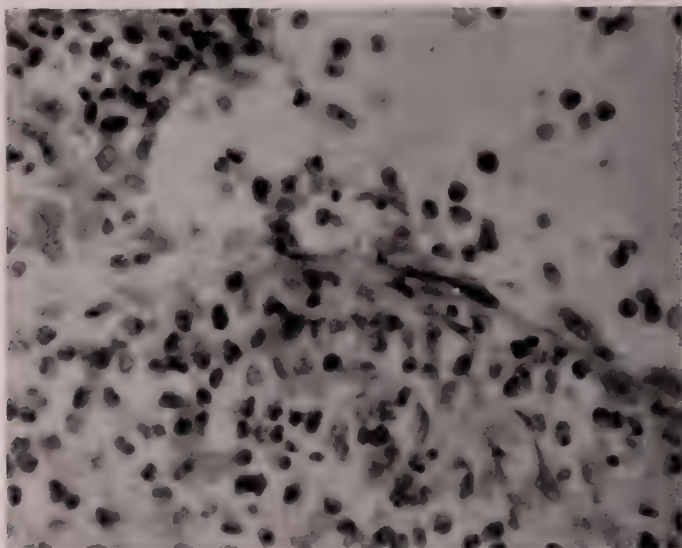


FIG. 16. Exudative inflammation; massive eosinophilic infiltration: Upper right hand corner shows lining of a dilated lymphatic vessel, eosinophils in great number are seen in and outside the vessel, mixed with lymphoid cells and fibroblasts. Hematoxylin-Eosin.

The two cases with mild inflammation showed intact worms only and conformed to the descriptions of lesions in early reversible filarial swellings (2, 3, 4). Of the 13 cases showing marked and widespread inflammation, five also showed fibrinous or fibrino-hemorrhagic vaginalitis (Fig. 12) at the level of the cord or epididymis or both. Three of these cases also showed an acute interstitial orchitis of peculiar type characterized by intense inflammatory edema with relatively

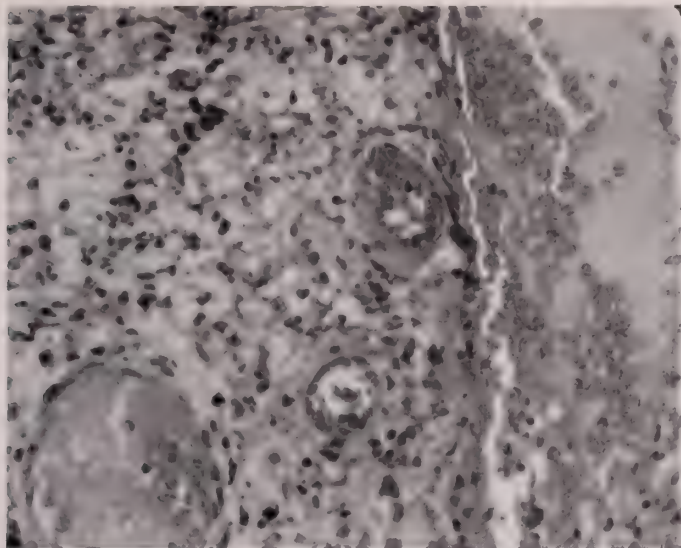


FIG. 17. Exudative inflammation; neutrophils and red cells: Near tunica vaginalis covering epididymis there is dense neutrophilic infiltration, blood vessels are dilated and there is recent hemorrhage into the serosal cavity. This was one of the cases with evidence of bacterial superinfection. Hematoxylin-Eosin.

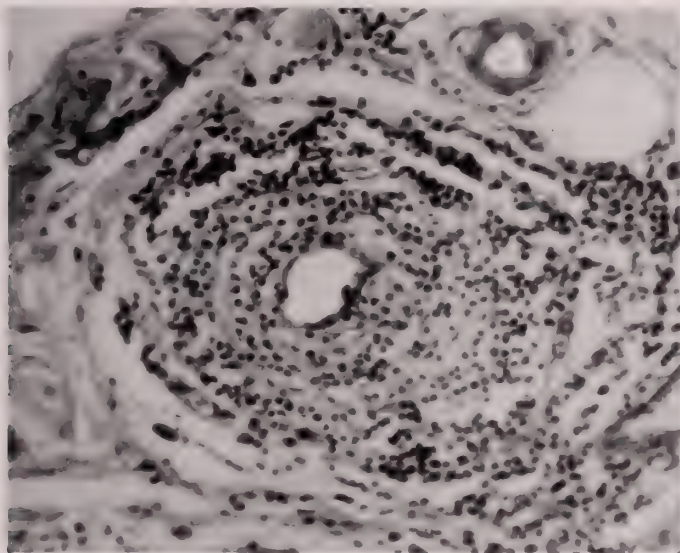


FIG. 18. Exudative inflammation; lymphoid cells. A small dilated lymph vessel of spermatic cord is surrounded by a dense aggregate of lymphoid cells. Hematoxylin-Eosin.

few leukocytes, mostly eosinophils (Figs. 13, 14) and with little damage to the germinal tubules.

The inflammatory exudate varied in composition. As a rule it contained more abundant intercellular than cellular material, and its most constant feature was a pale staining basophilic or amphophilic edema-like substance. In addition

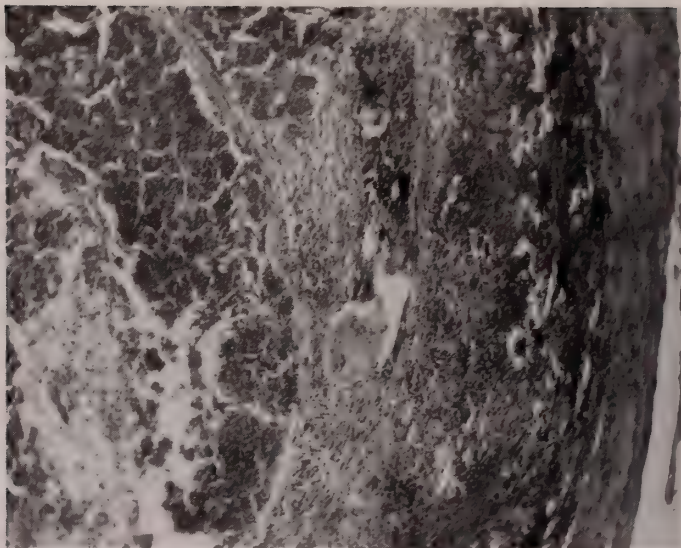


FIG. 19. Case with massive hemorrhage: Torsion associated with filariasis? Lymph vessels with lymphangiohemorrhage on left side. Interstitial hemorrhage on right, covered by tunica vaginalis. Exudative inflammation is seen between hemorrhagic areas. Hematoxylin-Eosin.

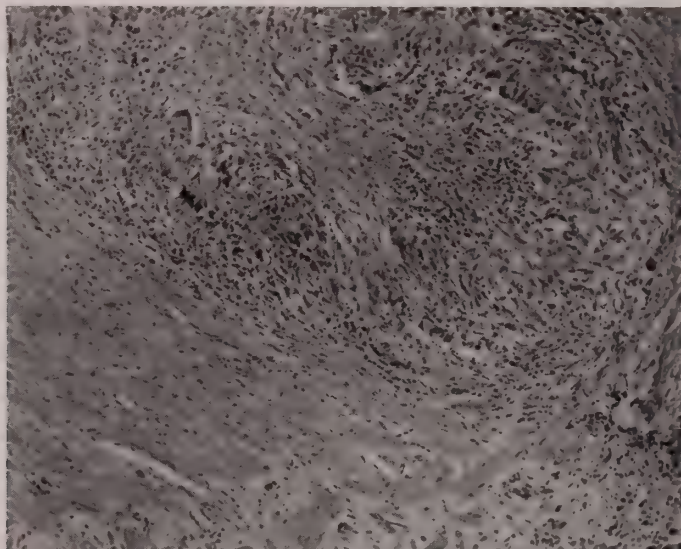


FIG. 20. Case with intensive granulomatous inflammation: Hyperergic reaction to filarial worm? Photograph shows granuloma in the wall of a large vein. The central portion of the granuloma is necrotic and shows fibrosis. Epithelioid and giant cells as well as lymphoid cells are present in the granuloma. Hematoxylin-Eosin.

there was focal deposition of fibrin (Fig. 15) (7 cases), red cells (4 cases) or both (6 cases). Of the inflammatory cells eosinophils predominated in 18 cases, (Fig. 16), neutrophils in three cases (Fig. 17) and lymphoid cells in the remaining three (Fig. 18). Massive tissue eosinophilia was seen in two instances.

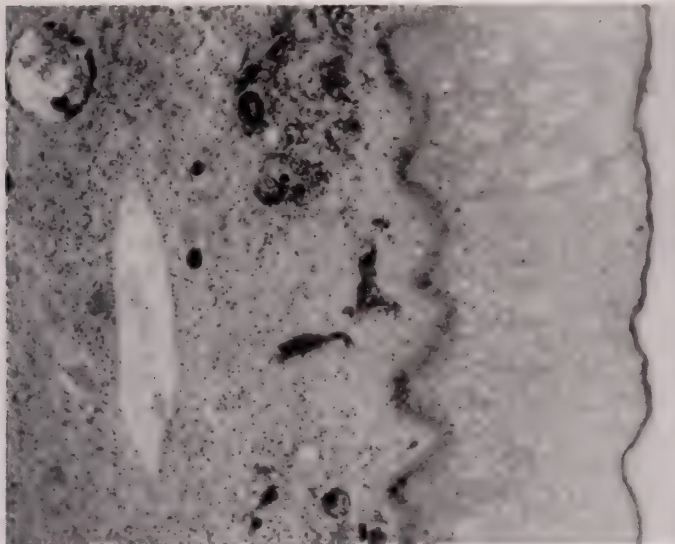


FIG. 21. Case with bacterial superinfection: Scrotum; epithelium shows edema and spongiosis; corion shows dilated lymph vessels and capillaries, minute hemorrhagic foci and spreading inflammatory infiltration with numerous polys, of phlegmonous type. Hematoxylin-Eosin.

Formation of fibrous tissue in the cord or epididymis occurred frequently even in lesions with recently damaged worms. In three cases there was marked diffuse fibrosis of the cord mixed with residual exudative inflammation.

IV. *Evidence of variability of the early tissue reaction.* A glance at the above data and at the microphotographs illustrating the lesions will be sufficient to illustrate the wide range of morphological changes observed in early filariasis. In addition to the variations already mentioned, there were five cases with lesions somewhat different from those described representing extreme degrees of such changes. One case showed massive hemorrhage both into lymph vessels and into the interstitium (Fig. 19), and the cord had become markedly swollen. It was suspected that in this case there had been torsion or trauma of the cord in addition to filariasis. Another case showed granuloma formation not only close to the worm and in lymph vessels, but disseminated in the connective tissue and in the wall of blood vessels. Some of these granulomas had giant cells and showed central necrosis (Fig. 20). These lesions seemed to illustrate an uncommon, 'hyperergic' or 'tuberculoid' tissue response to filariae. Finally, three cases showed violent acute inflammation with abundant fibrin and neutrophils, suggesting bacterial superinfection (Fig. 21) and in two of the cases there was thrombolymphangitis of septic type. One of the cultures taken from the inflamed area yielded gram negative bacilli of the *Coli-Aerogenes* group. No bacteriological study was done in the other cases.

DISCUSSION

The histopathological picture of early endemic genital filariasis is variable to such a degree that none of the alterations described here or in previous reports occur constantly enough to be considered as pathognomonic and the worm itself

must remain the final diagnostic criterion. Granulomatous lymphangitis can be regarded as presumptive evidence of filarial etiology (2, 3, 9), particularly if accompanied by other less characteristic lymph vessel alterations, and by an edema-rich exudate containing eosinophils. By these criteria, close to 40% of the lesions examined here would have been recognized as filarial, if the worm had not been found. It is to be noted, that the above considerations apply to acute and subacute lesions, and not to long standing chronic cases in which filarial lesions are residual rather than active, and the histological alterations are usually non-specific (6).

The finding of disseminated lymph and blood vessels damage and of spreading exudative inflammation in some cases of early endemic filariasis are considered important from the point of view of pathogenesis and of clinicopathological correlations:

When intact worms only were present, lymphangiectasis was the predominant lesion and thrombolympfangitis was not observed (3). When the worm was damaged, thrombotic obstruction of lymph vessels occurred (Figs. 22A and B). These findings are in agreement with previous suggestions that the early, reversible tissue swellings of filariasis are associated with live worms whereas the later obstructive manifestations are due to disintegrating worms (2, 3, 4). The granulomatous form of thrombolympfangitis seemed to occur mainly in the vicinity of disintegrating worms, whereas at distant levels, the lymph vessels showed non-specific lesions. These findings make us visualize filarial lymphangitis as a spreading or "repant" process which occludes long segments of lymph vessels, extending through collaterals and possibly even arising in distant foci, although the latter contention is subject to confirmation by topographical study. In subcutaneous filarial lymphangitis an analogous spreading of the process can be directly observed in the form of so-called "ramazones" (5) and of "centripetal" spreading lymphangitis (4). Conceived in this manner, spreading lymphangitis provides an explanation of the fact that the destruction of even a single worm can produce lymph stasis, at least temporarily. It was assumed in the past that a single worm could occlude a limited portion of single vessels, and that lesions of increasing severity were caused by worms inhabiting large lymphatic trunks and the thoracic duct where they have never been demonstrated (16).

Special emphasis should be given to the vein damage in early filariasis which was mentioned neither by O'Connor and Hulse (5) nor by the investigators of early filariasis in U.S. soldiers (2, 3, 4) and to which only scattered references can be found. Photographs of damaged veins are shown and commented upon in the Atlas of Ash and Spitz (17). They are mentioned in endemic cases from the French colonial territories (18, 19) and in some of the older reports collected by us (6). Surgeons operating on filarial lesions of the genitals have long been aware of venous congestion and varicocele of the cord, even in early cases (1, 14). While the vein lesions described here can by no means be considered as specific or constant, they were sufficiently frequent to suggest that they may influence the course of the disease and contribute to the establishment of chronic edema, particularly when there is thrombophlebitis.

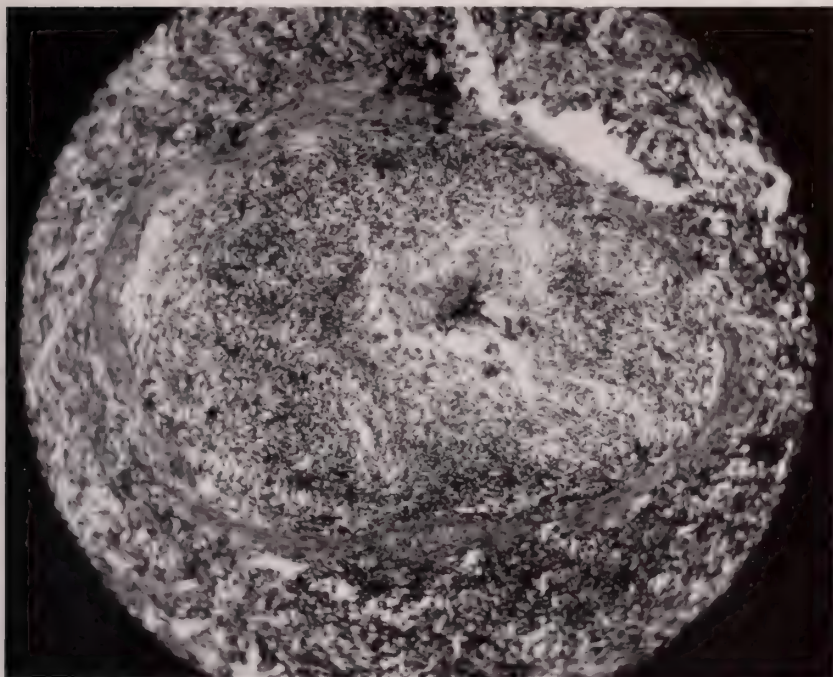


FIG. 22B

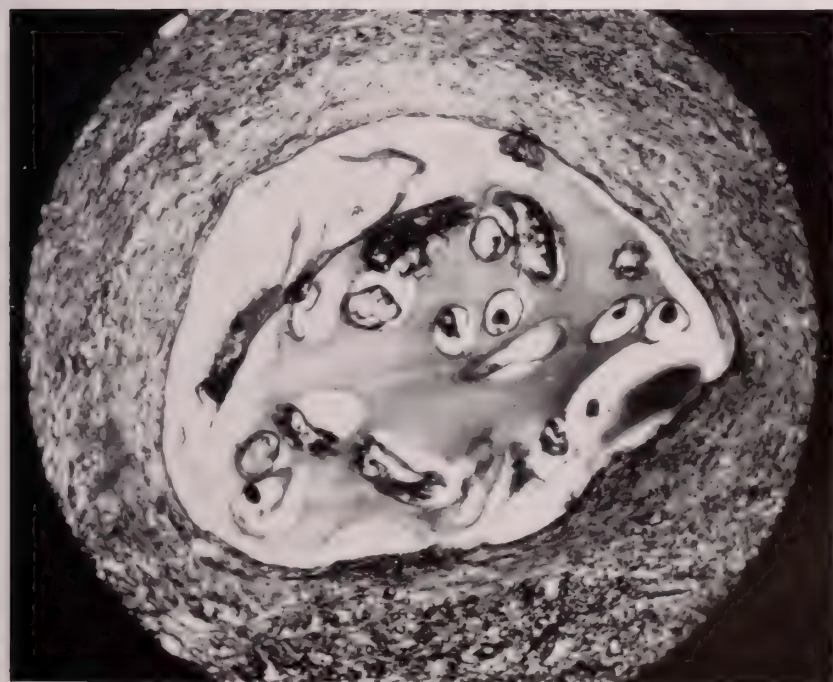


FIG. 22A

FIGS. 22 A and B. Reaction to live and to disintegrating worm. Both photographs were from the same case, and from adjacent zones. A shows the intact worm in a lymph vessel with lymphangiectasis, and without thrombosis. B shows rests of a disintegrating worm in a lymph vessel showing granulomatous thrombolympangitis. Hematoxylin-Eosin.

Exudative inflammation is mentioned in most reports on the pathology of filariasis. It has mainly been emphasized by Hartz and by Wartman (4, 15). Its frequency and severity in this material was surprising. Exudative inflammation is considered the histopathological counterpart of the rapidly installing tissue swelling during acute filarial attack, familiar to the clinician (1, 4). A double importance is attributed to this alteration. It may distend the tissue, and compress the lymph and congested blood-vessels, thereby promoting thrombosis. In addition, its richness in basophilic ground substance and its fibrin content would tend to elicit fibrogenesis, and thus facilitate the chronic edema and elephantiasis.

In the absence of experimental evidence, no explanation of the spreading exudative character of some early filarial lesions can be offered, but the following hypothesis is suggested: Assuming that the metabolic products of the adult worm have sensitized the tissues and often elicited fleeting hypersensitivity reactions (1, 3, 7, 20) and assuming further that during the early disintegration of the worm, the damaged parasite is not yet walled off by granulomatous tissue, there would occur a moment during which considerable amounts of disintegration products can reach the tissues; as these products are carried among lymph vessels, they would leave thrombolympangitis in their wake and their diffusion into the interstitium would produce exudative inflammation. This process can be interpreted as generically related to, but not necessarily identical with the Arthus phenomenon. At the early peak of the filarial attack the vessels are obstructed, the tissues infiltrated, distended and compressed and thrombophlebitis may occur. Later the worm is walled off by a granuloma, eventually to be destroyed or calcified. The vessels recanalize. The exudative changes recede, either toward resolution or toward fibrosis. As other worms die, filarial attack will subsequently recur, new active lesions will overlap with healing and scarring, and damage will eventually become irreversible. The later obstructive lesions of filariasis will show few active and specific lesions but many sequelae of scarring and healing, somewhat similar in nature to the "tertiary lesions" of other inflammatory diseases. Additional evidence favoring this concept will be advanced elsewhere.

Two fundamental criticisms can be leveled against the hypothesis given above: Absence of experimental proof is its most serious defect (21). The other argument is the lack of uniformity of filarial lesions evidenced in this material. This objection gains additional weight when it is considered that the cases represented a selection of severe lesions. Since the majority of endemically infected patients show a carrier stage rather than clinically active disease (5, 22), and since most of the U. S. soldiers with early filariasis failed to develop clinical sequelae (23), it is probable that the widespread exudative lesions seen here do not always occur and that in mild infections there is minimal inflammation leaving small, latent filarial foci, such as were found in abdominal surgery (16) and in autopsy cases (6). Such mild cases are becoming increasingly frequent in Puerto Rico (24). On the other hand, an explanation must be found for especially severe lesions. One of the cases observed here showed extensive granuloma formation and tissue response was considered as "hyperergic". If hypersensi-

tivity plays a central role in filarial pathology as has been contended (4, 7, 22), one would expect great individual variations in severity and type of tissue response and, in effect, such variability was seen to occur. Other variations in pathology appeared to be induced not by filariasis per se, but by complicating factors. While it was shown in U. S. soldiers, that bacteria do not play a role in early filariasis (4), it is reaffirmed here that bacterial superinfection does occur in endemic genital filariasis and may lead to septicemia and death (13). Infection and other complicating and accessory factors are thought to play an even greater role in the late chronic endemic lesions and to obscure their manifestations (6).

When comparing material from early endemic lesions with reports of material from early lesions in U.S. soldiers, basic similarities were noted: In both there were early fleeting lesions, associated with live worms, next there were thrombolymphangitic lesions due to disintegrating worms, with marked exudative inflammation and with tissue changes suggestive of hypersensitivity. Granuloma around the worm and scarring were seen next, and the lesions had a definite tendency toward fibrosis. The main differences were the greater frequency of severe lesions in the endemic cases and the occasional finding of early bacterial superinfection.

The next task will be to study the late and chronic forms of filarial disease in the light of the above findings, investigating both latent and asymptomatic sequelae and clinically active lesions. It is hoped that such a study will succeed in establishing a pathological background for the three stage concept of Bancroft's filariasis proposed by Manson-Bahr (22) and that an orderly and meaningful presentation of filarial pathology may thus become possible.

SUMMARY

In 24 cases of early endemic genital filariasis, attention was focused on lymph vessel damage, exudative inflammation and on vein damage. The incidence and histological aspects of these lesions were described.

While intact worms were not seen to produce lymph vessel thrombosis and the inflammation surrounding them tended of a mild and fleeting character, disintegrating worms were associated with thrombolymphangitis of a spreading or reptant type and, in general, with marked exudative inflammation and fibrosis. The thrombolymphangitis tended to be histologically granulomatous in the vicinity of disintegrating worms and histologically non-specific in more distant areas. Thrombophlebitis was seen in over one third of the cases. Exudative inflammation was marked and widespread in over one half of the cases. The endemic lesions were more frequently severe than those described in early filariasis of U.S. soldiers and, in three of them, there was histological evidence of bacterial superinfection. In general, the histological picture of endemic genital filariasis was highly variable and several cases showed extreme or individual types of lesion.

The significance of these findings is discussed with special attention to clinico-pathological correlation and to pathogenesis. Support is given to the hypothesis that tissue hypersensitivity plays an important part in filarial disease. It is

proposed that the pathological pictures seen in endemic genital filariasis can be ordered into three stages corresponding to the clinical stages of filarial disease suggested by Mason-Bahr.

ACKNOWLEDGMENT

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ISOLATED MYOCARDITIS: A REPORT OF NINE CASES

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In the course of three years (1953–1956) a number of cases were observed in the necropsy material of the San Juan de Dios Hospital, Bogotá (Colombia) which had in common certain pathological changes in the heart, especially in the myocardium, the etiology of which was not apparent. It was thought of interest to study these cases in an attempt to define their nature and, possibly, their cause. After having excluded cases of rheumatic heart disease, diphtheria, arterial hypertension and other conditions which lead to well known cardiac changes, there remained a group of nine cases which form the subject of this paper. In some of these, the cardiac lesions were inconspicuous and did not lead to heart failure. Nevertheless they were included as it was believed that they might be the initial phase of a condition, which, if given time to develop, would lead to more severe myocardial changes and give rise to cardiac insufficiency.

CLINICAL DATA

The clinical data, many parts of it were lacking or insufficiently reported, will be presented partly in tabulated form. The material of nine cases comprises eight males and one female from 15 to 48 years of age. All had lived most of their lives in tropical or subtropical climates. They were all of a poor economic class and had suffered throughout their lives from malnutrition so common in the lower classes in Colombia. The diet of this group is very poor in animal proteins and in certain vitamins and consists mainly of carbohydrates. They also consume an alcoholic beverage called guarapo obtained by fermentation of sugar cane syrup. This faulty nutrition is found in other underdeveloped countries, in Africa for example, as stated by Gillanders (1) and Higginson et al. (2) who studied cases similar to those analyzed in this paper. The patients of the present report belonged to ethnical group called mestizo, i. e. a mixture between white, predominantly Spanish immigrants and native Indians.

LABORATORY DATA

In four patients whose feces were examined for parasites mainly *Endamoeba histolytica*, *Necator americanus*, *Trichuris trichiura* and *Ascaris lumbricoides* were found alone or combined.

Red and white blood cell counts were performed in seven cases. Moderate to severe anemia was present in five patients and a slight leucocytosis in one. Two patients had a slight eosinophilia (up to 17 per cent). The differential counts were otherwise normal.

The erythro sedimentation rate was accelerated in three out of five patients tested.

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TABLE I

Age groups

10-19 years	1
20-29 years	2
30-39 years	4
40-49 years	2

TABLE II

Clinical manifestations

Cardiomegaly	5
Hepatomegaly	3
Dyspnea	7
Edema	5
Heart findings (ECG only taken in 3 cases)	
Tachycardia	6
Ventricular premature contractions	3
Bundle branch block	2
Cardiac murmurs	3
Cyanosis	6
Depressed blood pressure	2
Pulmonary findings	
Basal rales	4
Cough with sputum	5
Hydrothorax	6
Other findings	
Ascites	7
Jaundice	2
Splenomegaly	4

Wasserman and Kahn tests were negative in six patients on whom these were done.

The plasma proteins were determined in two patients. These showed a decrease in total proteins and inversion of the A/G ratio.

Other laboratory tests were performed only sporadically and were noncontributory.

CLINICAL DIAGNOSIS

In five patients congestive heart failure of unknown etiology was diagnosed, in three of these one of the following underlying conditions were considered: Fiedler's myocarditis, adhesive pericarditis and beriberi. Other additional diagnoses were: chronic malaria, malnutrition and secondary anemia. In two patients the diagnosis of shock due to intestinal obstruction and ileus was entertained and one was thought to have a brain abscess and circulatory collapse.

PATHOLOGICAL FINDINGS

External examination and serous cavities revealed poor nutritional condition in most of the patients. There were subcutaneous edema and serous fluid effusions almost in each.



FIG. 1. Case 3. Heart, showing hypertrophy and dilatation of right cavities.



FIG. 2. Case 8. Heart, showing hypertrophy and dilatation of right cavities and thickening of the endocardium.

The heart was slightly to severely enlarged in eight patients. This enlargement was due to myocardial hypertrophy and to dilatation of chambers, usually more marked on the right than on the left side (Figs. 1 and 2). In the majority of the cases the myocardium was described as pale and flabby. In one there was endocardial fibroelastosis with subendocardial fibrosis (Fig. 2). Two hearts showed mural thrombosis with fibrous thickening of the endocardium where the thrombi were attached. In some cases "tigering" due to fatty change of the myocardium was seen through the endocardial lining. Occasional flecks of fibrosis of the myocardium were visible to the naked eye. The valve rings and their appendages were normal in all cases. The coronary arteries, including their ostia usually were normal. Atheromatous patches were seen but were so small and scanty as to be of no importance.

Microscopically the changes varied considerably in severity ranging from

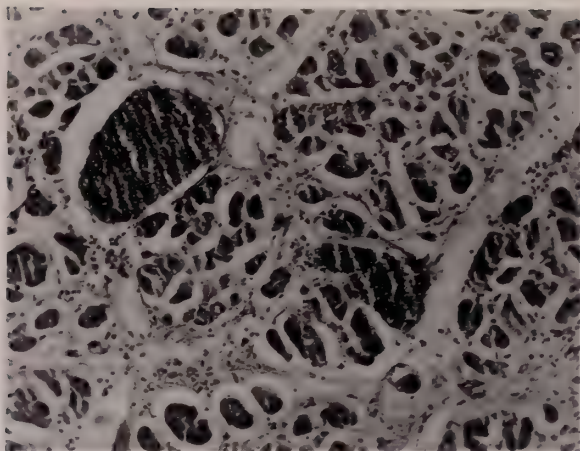


FIG. 3. Myocardium, showing dilated capillaries, edema, leucocytic infiltration and diffuse fibrosis. H. and E. $\times 105$

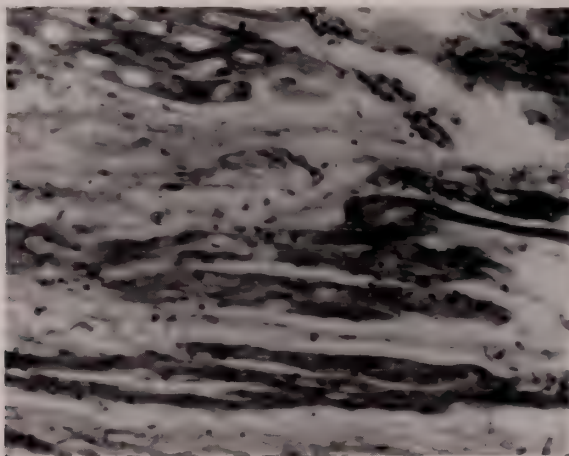


FIG. 4. Myocardium, showing vacuolization and destruction of muscle fibers. H. and E. $\times 360$

marked edema to a diffuse myocarditis. The changes most commonly found were a striking dilatation and engorgement of small veins and capillaries (Fig. 3). Striking interstitial and intracellular edema was usually present with vacuolization of muscle fibers (Figs. 4 and 5). In most of the cases there was a nonspecific interstitial inflammatory exudate consisting mainly of lymphocytes and occasional plasma cells, polymorphonuclear leucocytes and hystiocytes (Fig. 6). In no case was there a large number of eosinophils. Occasional granulomata with multinucleated giant cells of muscle origin were present in one heart (Fig. 7), associated with marked fibrous thickening of the endocardium and fibrosis of the subendocardial muscle. In almost all instances there were small interstitial and perivascular patches of fibrosis in the myocardium. In some cases the fibrosis was diffuse (Figs. 8 and 9). The muscle fibers showed the following alterations:

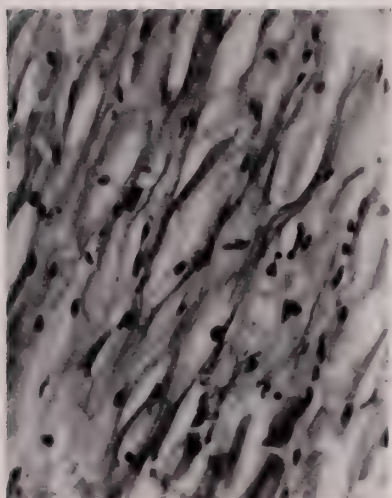


FIG. 5

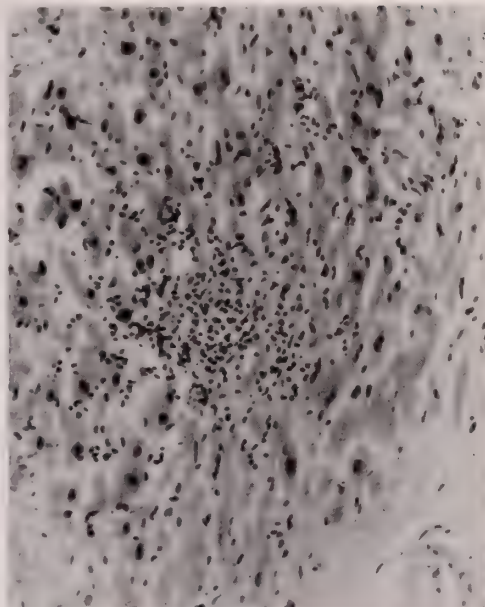


FIG. 6

FIG. 5. Myocardium, showing vacuolization of muscle fibers. H. and E. $\times 1050$

FIG. 6. Myocardium, showing focal and diffuse infiltration by inflammatory cells. H. and E. $\times 350$

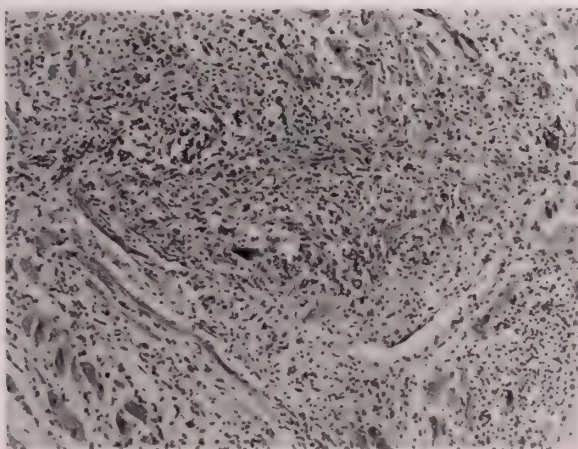


FIG. 7. Myocardium, showing a granulomatous lesion. One giant cell is present. H. and E. $\times 105$

in some cases there was fragmentation and vacuolization, loss of striations and a granular appearance of the cytoplasm (Fig. 5). Small sudanophilic fat droplets were found in four cases. Increase of lipofuscin pigment was often observed. In most instances there was hypertrophy of muscle fibers. There was no necrosis of muscle. The process described was diffuse throughout the myocardium of both

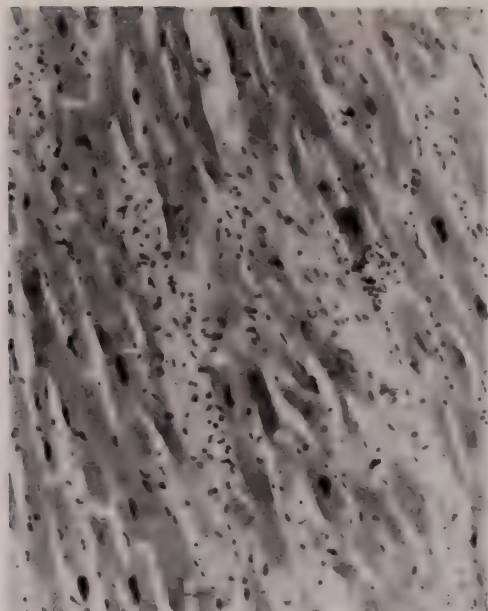


FIG. 8. Myocardium, showing patchy fibrosis and leucocytic infiltration. H. and E. $\times 550$

ventricles. There was no evidence of a specific infection and no microorganisms were found in sections. The mural thrombi were in varying phases of organisation. In some cases the epicardium also showed inflammatory change.

Main blood vessels. There was only a moderate degree of atheromatosis of the aorta and the collateral branches. In one case there was thrombosis of the femoral veins.

Lungs. There was moderate to severe edema and congestion of both acute and chronic duration. Infarcts were found in two cases who had mural thrombi in the right heart. The pulmonary arteries were normal.

The spleen was enlarged in five cases. These presented fibro-congestive splenomegaly. Some of the larger spleens belonged to patients who were said to have had malaria in their past. Malarial pigment could be demonstrated in only two of these spleens; malarial parasites were not found. The remaining spleens showed simple congestion without fibrosis. Small healed or healing splenic infarcts were present in two instances.

The pancreas showed no significant changes in three cases, five showed slight interstitial fibrosis with sparse infiltration of leucocytes. In one a rather severe acute and chronic pancreatitis with foci of fat necrosis was present. No correlation of these changes with the clinical picture could be established.

The liver was significantly enlarged in three cases and within normal limits of weight in the remaining cases. In four a "nutmeg" liver was described grossly. Microscopically all showed centrilobular congestion, which tended to be very severe with central necrosis and fatty change of moderate degree. "Cardiac fibrosis" was seen in three cases. Two showed a marked increase of inflammatory cells in the portal tracts and in the capillaries with presence of abundant bile

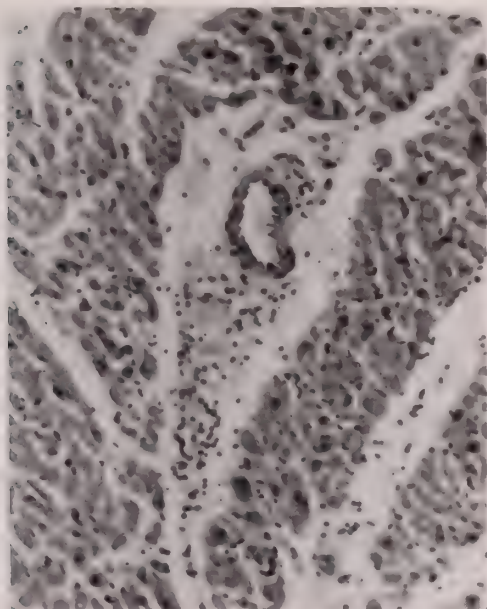


FIG. 9. Myocardium, showing small artery with perivascular fibrosis and inflammatory exudate. H. and E. $\times 350$

pigment in the liver cells and bile thrombi in the canaliculi. Both these patients were jaundiced, and one had received an incompatible blood transfusion a few days before death.

Gastrointestinal tract. In three cases there was marked dilatation of intestinal loops; two of these had clinical signs of paralytic ileus. One or more kinds of intestinal parasites were found in almost all cases, the most frequent being hookworms and whipworms. In one case the former had given rise to multiple small submucosal abscesses in the jejunum. In one subject there was a severe chronic ulcerative esophagitis. A slight nonspecific colitis with numerous eosinophils was frequent. One had a chronic peptic gastric ulcer.

The adrenals were normal in most of the subjects. In one, small foci of necrosis with leucocytic infiltration were found, another one showed small foci of lymphocytes. Cortical atrophy was described in two.

The kidneys showed small healed infarcts in one patient. All were congested. In two a moderate number of hemoglobin casts were present in the distal tubules, attributed in one to the incompatible blood transfusion. In three there was a slight pyelitis.

Other significant findings. In one of the two icteric patients numerous petechiae and visceral hemorrhages were found. One patient had several large brain abscesses and another a nodular goiter.

COMMENTS

The presented cases show some features in common which are thought to have a bearing on the etiology of the cardiac changes. There was a strong preponder-

ance of males over females (8:1); the oldest was 48 years of age but most of them were in the third decade. It has been mentioned that they all were mestizos, subject to chronic malnutrition and dwelling in tropical or subtropical areas. Most of them were parasitized by hookworms and other species, some had had malaria and five were moderately to severely anemic. The plasma proteins where determined were abnormal. The etiology of the cardiac abnormalities could not be traced to infectious diseases, and it is improbable that chronic malaria from which some patients had suffered could have been directly responsible for the heart condition. No microorganisms were found in the sections. There was no evidence of an allergic process. The coronary arteries were either normal or showed minimal atheromatosis without encroachment on the vessel lumen. The changes in the heart were not specific. Edema usually was severe, interstitial and intracellular with vacuolisation and atrophy of muscle cells. Fine fat droplets were present in some of the cases. Groups of fibers had disappeared and instead patches of fibrosis were present. The severe inflammatory reaction was striking in most cases and was diffuse and predominantly lymphocytic in type.

On analyzing these pathological changes it appears that the present cases should be classified as an isolated, diffuse myocarditis. Saphir (3) considers this as one of the types of myocarditis but stresses the point that it is by no means specific. He mentions the possibility that it might begin as a serous inflammation as conceived by Eppinger, Kaunitz and Popper (4). The extravasated plasma would be injurious to the tissues and thus give rise to the formation of connective tissue. Pirani (5) found a high incidence of serous myocarditis in cases of human starvation.

In a series of 1,402 cases of myocarditis, Saphir and Gore (6) found that 90 per cent of cases were non-rheumatic, indicating that this condition is not so rare as is commonly believed. The myocarditides in these writers' cases were associated with a wide variety of diseases and conditions: exposure to toxic substances (as in diphtheria), physical or chemical agents (as carbon monoxide poisoning), viral, rickettsial and fungus diseases, various metabolic states, hypersensitivity and inanition. Among 50 cases of starvation 33 had myocarditis.

Gillanders (1) and Higginson et al (2) in Africa studied "nutritional heart disease" in 30 Bantu patients 22 of whom were males. Their diet was similar to the one of the patients mentioned in this paper and consisted mainly of maize, bread and sugar, few vegetables and fruit and no meat or milk. Thiamin alone did not improve the clinical picture but an adequate diet did in some patients. Necropsy findings were enlargement of the heart without valvular lesions or fibroelastosis. Microscopically they stressed the presence of small diffuse areas of fibrosis and occasionally infiltration by mononuclear cells. The pictures in their article show similar lesions to those found here but with less severe inflammation and less destruction of muscle fibers.

The severe dilatation and hypertrophy, especially of the right ventricle with hydropic changes in the muscle fibers in some cases, recall the so called beriberi heart. However there seems to be no agreement among the different observers as

to the typical changes in this condition. Griffith (7) who studied the heart in beriberi and malnutrition, did not find a specific picture in his cases. He reviewed the literature in which the following changes were mentioned in the beriberi heart: hypertrophy, dilatation, hydropic degeneration of fibers, interstitial edema, replacement fibrosis, loss of striations of muscle fibers and lymphocytic and leucocytic infiltration. The hearts described in this article showed most of these changes.

Experimentally, lesions in the myocardium have been caused by special diets. Thus Thomas, Mylon and Winternitz (8) produced severe myocardial lesions characterized by necrosis of muscle fibers and marked, chiefly mononuclear cell infiltration in rats and hogs fed a diet deficient in potassium and vitamin B₆. Jaffé et al. (9) produced myocardial lesions in rats subjected for some weeks to a diet low in vitamin B₁. This was repeated several times at intervals of one month. The authors believed that an allergic process was responsible since a single period of diet failed to produce myocardial alterations. The changes consisted in neorobiosis and small infiltrations of round cells.

Gopalan (10) in a clinical analysis of 600 cases of heart failure in India found a high percentage (14.4 per cent) which did not fall under any of the well established categories of diseases like rheumatic fever, syphilis etc. These cases were drawn from a community in which kwashiorkor and nutritional edema are common. Gopalan therefore seriously considers a nutritional basis for at least some of these cases.

Bras (10) and Trowell et al. (11) did not find significant changes in the hearts of children with kwashiorkor. Malnutrition of long standing may be required for myocardial lesions to develop.

The association of so called endocardial fibrosis with severe myocarditis showing occasional granulomata in one of the presented cases is of interest. This appears to be infrequent as usually inflammation of the myocardium is not accompanied by endocardial fibrosis. The etiology of fibroelastosis is still unknown; theories which have been advanced in the adult form include syphilis, malnutrition, vitamin deficiencies, trypanosomiasis and hypersensitivity. Gray (12) who studied patients in West Africa believes in an infectious or parasitic cause, as eosinophilia was frequent in his cases. This was not true in the presented material. It is felt that the alterations of the endocardium may be caused by variety of mechanisms.

It is of interest to note that Brass (13) in Venezuela found chronic myocarditis in 38 per cent of all adult patients studied at necropsy. He did not consider malnutrition an important factor. Subsequently Maekelt and Lopez (14) working in the same hospital found in 37 patients out of a nonselected group of 100 a positive complement fixation test for Chagas' trypanosomiasis. Thirty-two of these patients suffered from heart disease. Four had died by the time the authors' article was published and post mortem examination revealed a chronic myocarditis which was thought to be a chronic form of Chagas' disease. The complement fixation test for this malady was not done in the present group of patients. This test may be of value in Colombia in patients with congestive

heart failure of unknown cause, since *Trypanosoma cruzi* and the transmitting insects exist in this country. It is felt however, that the presented cases are not trypanosomiasis as neither parasites nor parasitic granulomata were present and because the degenerative muscle changes described here are not a feature of Chagas' disease.

In concluding one can say that the cardiac lesions encountered in this group of cases were non specific. Histologic studies did not lead to recognition of the cause of the myocardial alterations. Malnutrition, including vitamin deficiencies, was common to all the cases and its importance in the etiology of this form of heart disease should be taken into consideration.

The mechanism by which the lesions are produced is not understood. The absence of certain dietary factors indispensable for the integrity of the heart muscle, together with chronic anemic hypoxia may lead to edema, destruction of muscle fibers, inflammation and replacement fibrosis. Hypertrophy of the myocardium with its increased demand for oxygen may lead to more anoxia. A similar mechanism has been postulated by Elster et al. (15) in the study of the so-called cardiac hypertrophy of unknown etiology.

It is hoped that further studies of the pathology of this condition as well as of the environmental, dietary and parasitic factors will lead to a better understanding of this and similar conditions of the heart.

CASE REPORTS

Case 1

Male, 15 years, semicomatose on admission, severe anemia, weak heart sounds, hypotensive, dyspneic, marked abdominal distension, liver and spleen not felt, oliguria, no edema, afebrile. Remained stuporous and died shortly after admission. Total length of illness not known.

Clinical diagnoses: Paralytic ileus, anemia of unknown origin.

Main pathological findings: anemia, myocarditis (acute diffuse), bronchopneumonia, generalized visceral congestion, malaria?

Case 2

Male, 38 years, five months illness with productive cough, dyspnea and fever. Previous illnesses: Malaria, dysenteric syndrome. Physical examination: Pale, malnourished, slightly jaundiced, dyspneic, weak heart sounds, normotensive, febrile, palpable spleen, liver not felt. Died six weeks after admission with hemorrhagic diathesis and jaundice, possibly related to an incompatible blood transfusion. Total length of illness: approximately seven months.

Clinical diagnoses: Chronic malaria, secondary anemia, malnutrition.

Main pathological findings: Hepatomegaly (1845 grams), malarial splenomegaly (1130 grams), hemolytic anemia, hemoglobinuric nephrosis, myocarditis (chronic, diffuse), pulmonary edema.

Case 3

Female, 38 years, admitted in congestive heart failure. Patient dyspneic, cyanotic, anasarca, heart enlarged, weak heart sounds, hypotensive, moist basal

rales, ECG: ventricular premature contractions, right ventricular hypertrophy, right bundle branch block. No improvement with digitalis; died in congestive heart failure. Total length of illness: 18 months.

Clinical diagnosis: Congestive heart failure of unknown cause.

Main pathological findings: Myocarditis (chronic, diffuse), cardiac hypertrophy and dilatation, especially right ventricle (heart weight 395 grams), mural thrombosis both ventricles, pulmonary infarcts, renal infarcts (healed), hydrothorax (bilateral), ascites, chronic passive congestion of viscera, especially of the liver.

Case 4

Male, 20 years, admitted because of left sided hemiplegia of one month duration. Clinical findings compatible with lesion of the right cerebral hemisphere, weak heart sounds, afebrile. Shortly before death developed circulatory collapse. Previous illnesses: malaria, dysentery. Total length of illness: five months.

Clinical diagnoses: Brain abscess, malnutrition, chronic malaria.

Main pathological findings: Brain abscesses (right frontal lobe and cerebellar hemisphere), malarial splenomegaly (360 grams), hepatomegaly (1,565 grams), myocarditis (chronic, diffuse) pulmonary edema.

Case 5

Male, 48 years, congestive heart failure of two months duration. Previous history: malaria, suppurative inguinal lymphadenitis. Physical examination: dyspneic, cyanosed, hypotensive, weak heart sounds, tachycardia, systolic murmur at apex, heart enlarged, distended neck veins, moist basal rales, subcutaneous edema, ascites, hepatomegaly. ECG: ventricular premature contractions, myocardial damage. Developed pulmonary infarcts and died in congestive heart failure. Total length of illness: four months.

Clinical diagnosis: Congestive heart failure, Fiedler's myocarditis?

Main pathological findings: Myocarditis (chronic, diffuse), hypertrophy and dilatation both ventricles (heart weight 500 grams), ventricular parietal thrombosis (bilateral), pulmonary edema and infarcts, splenic infarcts, chronic passive congestion of viscera, necrotic enteritis with submucosal abscesses in jejunum, acute and chronic pancreatitis (moderate), chronic malaria?

Case 6

Male, 48 years, admitted in decompensated congestive heart failure of 6 months duration. Previous illnesses: Malaria, dysenteric syndrome, malnutrition. Physical examination: anasarca, dyspneic, cyanotic, enlarged heart, weak heart sounds, hypotensive, hepatomegaly, splenomegaly, ascites, oliguria, afebrile, ECG: Ventricular premature contractions, myocardial damage, 2:1 A V block. Died shortly after admission. Total length of illness: seven months.

Clinical diagnoses: chronic malaria, malnutrition, congestive heart failure, beriberi heart?

Main pathological findings: Myocarditis (chronic, diffuse), hypertrophy and dilatation of both ventricles especially of the right (heart weight 450 grams),

chronic passive visceral congestion, small splenic infarcts, ascites, hydrothorax, hydropericardium.

Case 7

Male, 34 years, admitted with severe, diffuse abdominal pain and distension, abdominal silence on auscultation, severe anemia, heart sounds normal, tachycardia, afebrile, malnutrition. Died few hours after admission. Length of illness not known.

Clinical diagnosis: intestinal occlusion and paralytic ileus.

Main pathological findings: hypertrophy and dilatation both ventricles, especially right (heart weight 385 grams), myocarditis (diffuse), pulmonary edema, chronic passive visceral congestion, intestinal distension of unknown cause, infestation with *Necator americanus*.

Case 8

Male, 26 years, admitted in severe congestive heart failure of 15 months duration. Previous illnesses not known. Father died of heart failure. Patient severely dyspneic, cyanotic, distended neck veins, productive cough, weak heart sounds, heart enlarged, normotensive, moist basal rales, ascites, hepatomegaly, no edema, afebrile. Thoracotomy because of clinical diagnosis of adhesive pericarditis was done and a hydropericardium with some adhesions found. Heart markedly enlarged. Died in post operative shock. Total length of illness: two years.

Clinical diagnosis: Congestive heart failure of unknown etiology.

Main pathological findings: Myocarditis (chronic, diffuse), hypertrophy and dilatation of both ventricles (heart weight 470 grams), endocardial fibrosis, chronic passive visceral congestion, ascites, hydrothorax (bilateral), infestation with *Necator americanus*.

Case 9

Male, 37 years with congestive heart failure of one month duration. Physical examination: pale, dyspneic, weak heart sounds, tachycardia, ascites, subcutaneous edema, afebrile, precordial and epigastric pain. Died shortly after admission in circulatory failure. Total length of illness: five weeks.

Clinical diagnoses: Congestive heart failure, malnutrition.

Main pathological findings: Myocarditis (chronic, diffuse), slight hypertrophy and dilatation of both ventricles (heart weight 310 grams), chronic passive congestion of viscera, ascites, hydrothorax (bilateral).

SUMMARY

Nine patients, most of them dying in heart failure of unknown cause, are presented. Necropsy revealed myocardial changes which in most cases can be classified as an isolated, diffuse myocarditis. The lesions ranged from severe edema and hydropic degeneration of muscle fibers to a most severe, diffuse infiltration by inflammatory cells and patchy fibrosis, associated in one case with endocardial fibroelastosis.

Common etiologic factors like coronary arteriosclerosis, hypertension, syphilis and rheumatic fever were excluded. All the presented cases belonged to the same ethnological group called mestizo and had lived in tropical or subtropical climate in Colombia under poor dietary conditions.

The findings of several investigators on similar patients have been reviewed and the possible etiologic factors briefly discussed.

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ON THE BACKGROUND OF THE DISCOVERY OF NEUROCHEMICAL TRANSMISSION

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In general one roughly distinguishes between scientific discoveries originating from chance, from deliberate analysis or from intuition. The discovery indicated in the title belongs to the last group (1-3).

It has become widely known that in 1921 I awoke one night with the complete design in my mind of an experiment that would prove, as in fact it did, (4), the occurrence of neurochemical transmission. I covered the story in a fairly detailed way in 1953 (5) but later I found that in that paper the presentation of the background of the discovery was incomplete. I intend to make up for the omissions, so that the occurrence of the discovery may appear less mysterious.

The concept of neurochemical transmission had first turned up as early as 1903 (5): while I discussed with my coworker Walter M. Fletcher the fact that stimulation of the vagus acts exactly like administration of the alkaloid muscarine, the idea suddenly occurred to me that the vagus might act by releasing from its endings a muscarinelike substance. It is not astonishing that this idea should have originated with a pharmacologist, because his thoughts and activities hinge almost exclusively upon effects of chemical substances. In addition my interest in this special problem had certainly been aroused or increased during a previous stay in Cambridge (England) by close contact with T. R. Elliott. Elliott then was comparing the effects of adrenaline with those of sympathetic nerves over a wide range of organs and species, and found a striking similarity (6).

So much for the background from which my original hypothesis might have emerged.

I now have to turn to the question of the circumstances and experiences that may have prepared my mind for designing the experiment which eighteen years later proved the correctness of my hypothesis. Only quite recently I found some clues which may serve as guides in the search.*

A few months ago I had to write my bibliography and for this reason glanced over all my papers and those of my former students. I noticed that not less than seven of these papers (7-13), published between 1905 and 1912, had dealt with problems connected with the physiology and pharmacology of the cardiac vagus. This indicates my intense interest in that nerve, which in 1921 I used as the object of my experiment.

In most of these studies and in many others I had used the well known Straub method, which also served in the experiment in 1921 (4).

Of much greater import, however, for the present inquiry is the methodical

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* The revival of my interest in this search was enhanced by a conversation with the psychoanalyst, Dr. Ernst Kris.

procedure applied in other studies (14) also preceding the experiment of 1921: in some of them it had been found that when a frog heart was filled with calcium free Ringer solution, its contractility decreased immediately to almost zero and then gradually recovered. To find out whether the recovery might have been due to a substance released from the heart into the medium, the medium was withdrawn during the recovery period and instilled into a heart depressed by calcium free Ringer solution. Contractility was immediately restored.

On the other hand, the neurochemical transmission was proven by the demonstration that the Ringer solution withdrawn during a period of vagus stimulation and applied to a normal heart, contained a substance that caused it to act, when applied to a normal heart, exactly like the nerve-stimulation. (4): This shows that the method I successfully used for tracing the "Vagusstoff" in the medium, was fundamentally identical with that applied in the previously quoted experiments for tracing another substance released from the heart into the medium. And two of these studies (15-16) only shortly preceded the arrival of the nocturnal design. This fact, in my opinion, was essential in preparing or triggering the concept of the finished design in my unconscious (preconscious) mind by reactivating there the basic hypothesis after its eighteen years of sleep. In fact the new concept represented a sudden association of this hypothesis with the idea of applying a method tested shortly before in other experiments.

For the time being one has to content oneself with the recognition of the sources to which unconsciously created associations can be traced. This recognition obviously does not contribute anything to the elucidation of the mode of activity of the unconscious mind. This activity, however, is alone responsible for the sudden birth of those associations which are characteristic of intuitive discoveries.

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THE PROTEIN FRACTIONS OF SYNOVIAL FLUID AND UMBILICAL CORD MUCIN¹

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Investigations of the chemical nature of the mucinous intercellular and inter-fibrillar amorphous substances of the connective tissue have heretofore been chiefly concerned with the polysaccharide portion of the material. Great effort has been expended to obtain these carbohydrates in pure form after the associated proteins had been removed, with the result that the latter have been given little notice. Recently, attention has been redirected to the proteins of the ground substance and particularly to the question of their relationship to the polysaccharides. Do the latter occur in a complex with the protein fraction or do they exist in a free, uncombined state? The mere fact that the proteins can be chemically separated from mucin solutions only with great difficulty suggests that they represent an integral part thereof. Evidence to support this viewpoint concerning the hyaluronate in synovial fluid has been offered by Ropes et al. (1) and by Ogston and Stanier (2, 3). Similarly, Partridge (4) has reported that chondroitin sulfate in cartilage is linked to collagen. Assuming that such complexes exist, it becomes important to determine the kind of proteins involved, in the hope of ascertaining the possible origin of this portion of the amorphous ground substance.

This paper is concerned with the identification of the proteins present in the mucinous materials obtained from bovine synovial fluid² and human umbilical cords. Experiments were carried out upon polysaccharide-protein complexes prepared in as undegraded a state as possible.

METHODS

Two sources were used to obtain mucoprotein needed for investigation. The first was bovine synovial fluid obtained either fresh from local slaughter-houses, or preserved under toluene; in either case its average viscosity at 39°C was 4.0 relative to water. The second source of mucin was human umbilical cords obtained immediately after delivery and freed of all blood. After centrifugation and filtration through glass wool to remove all particulate matter from the synovial fluid, mucin for most experiments was precipitated out of solution by acidification with acetic acid to pH 3.5. The mucin clot thus obtained was removed, washed several times, and dissolved in disodium hydrogen phosphate (M 20). After dialysis, the solution was acidified as before and the mucinous precipitate separated off, washed and lyophilized. Additional samples of mucin

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² Obtained through the courtesy of Mr. Jack Schmidt, of Armour & Co., N. Y. C.

from the same source were obtained by filtration through a very fine sintered glass funnel (max. pore diam. $1.2\ \mu$), the residue being washed and lyophilized.

For the preparation of mucin from umbilical cords, the latter were ground in a meat-grinder, and 150 grams extracted for 6–7 days at 5°C , either with a solution of calcium oxide (100 mg. in 400 ml. water), or with a potassium chloride solution (400 ml., $\text{N}/10$). Because of the duration of this procedure, the mixture was kept covered with a thin layer of toluene. The very viscous colorless supernatant liquid was separated by centrifugation and clarified by filtering through glass wool. It was dialysed against running water for 48 hours, after which time the liquid reached a pH of 7.4. Digestion with amylase to destroy all starches present (2–3 days) was followed by dialysis against water, and further treatment was that employed for the mucin obtained from synovial fluid.

For the hyaluronidase studies, representative samples (300 mg) of each batch of mucin were dissolved in an acetate buffer at pH 5 (150 ml.) and purified crystalline testicular hyaluronidase was added to produce a concentration of 1500 turbidity reducing units of enzyme (10 TRU/ml.). They were incubated at 37°C for 3 days and then dialysed against running water for 48 hours, to get rid of degradation products. Addition of 2 volumes of ethyl alcohol to the cold solution yielded white precipitates which were centrifuged off, washed with alcohol and ether, and dried in vacuo. Additional fractions of mucin (300 mg) were dissolved in phosphate buffer at pH 8 (150 ml) and digested with 30 mg of crystalline trypsin for 2 days. After this period, the same procedure as indicated above was followed. Some samples were subjected, in succession, to both hyaluronidase and trypsin, using enzymes in either of the two possible orders.

All specimens obtained in preceding paragraphs were analysed for their nitrogen and glucosamine contents. The nitrogen values were obtained through standard micro-Kjeldahl procedures, and glucosamine values through a modification of the Elson and Morgan method (5, 6). Samples from several of the products mentioned above were prepared for paper chromatography and paper electrophoresis by acid hydrolysis. To verify the completeness of the results obtained by this method of hydrolysis, and to ensure the recovery of all amino-acids present originally, other experimental procedures for hydrolysis were tried and results compared (7).

To standardize the amounts used in subsequent chromatography and electrophoresis, the products from hydrolysis were dried in vacuo, and aqueous solutions of constant concentration made. For chromatography of the amino acids, the standard 2-dimensional ascending method was used (8). The solvent for the first dimension was a water-saturated solution of phenol; a mixture of collidine, lutidine and water (10:10:11) was used for the second dimension. After this the sheets were dried in an oven at 100°C and the patterns developed by spraying them with a 0.1% solution of ninhydrin in *n*-butanol.

In an attempt to elucidate the protein-polysaccharide relationship, the electrophoretic behavior on paper of the various mucin specimens was investigated at different pH values. The apparatus was a modification of the type described

by Durrum (9, 10). By varying the voltage for each buffer the current could be maintained at 0.5–1.0 millamp. per cm. width of paper used. The material under examination was applied as a drop (5–40 ml) of solution in barbital buffer (4 mg. ml.), at the center of the paper strip. In most cases 5 hours were sufficient to give good separation of the components.

For electrophoretic separations in alkaline medium, an aqueous solution of sodium veronal (M 20) and veronal (M 100) at pH 8.6 was used. When behavior in acid medium was to be investigated, the buffer consisted of an aqueous solution of sodium chloride (0.15 M), sodium acetate (0.10 M) and acetic acid (0.1 M) and at pH 4.8. In a few experiments where a buffer of pH 7 was required, a M 15 solution of disodium hydrogen phosphate (6p.) and potassium dihydrogen phosphate (4p.) was used. Staining of proteins was carried out with brom-phenol blue (11), and that of hyaluronic acid and chondroitin sulfuric acid with toluidine blue, using standard procedures.

RESULTS

Two-dimensional paper chromatography did not provide sufficient data to characterize the proteins under investigation in terms of their amino acid composition. However, evidence of the presence of glycine, valine, threonine, leucine, and alanine in the material under investigation was obtained with this method. The presence of the aromatic amino-acids tryptophan and tyrosine was demonstrated by means of ultra-violet absorption curves of solutions of whole mucin; these were confirmed by means of the glyoxalic acid reagent and Millon's reagent, respectively. Paper electrophoresis of hydrolysates of mucin in buffers of varying pH was utilized to demonstrate the existence of glutamic and aspartic acid (at pH 4.8), lysine and arginine (at pH 8.6), and proline and hydroxyproline (at pH 2).

In an effort to obtain more definitive identification of the proteins present in the mucin complex, it was necessary to resort to methods other than those described above. Separation of the components of whole, undegraded synovial fluid mucin by paper electrophoresis was first attempted in veronal buffer at pH 8.6, well above the isoelectric point of the proteins present. The existence of 3 main fractions was revealed. (See Fig. I.) Two stained with brom-phenol blue, which identified them as proteins. The first of these remained at the point of origin (Fraction A), and the second presented a forked pattern migrating towards the anode (Fraction B). The third (Fraction C) did not stain with brom-phenol blue, but gave a metachromatic coloration with aqueous toluidine blue. It invariably appeared in close apposition to Fraction B, occupying the space between the branches of the fork. The identity of Fraction C with hyaluronic acid seems reasonable in view of the similarity of staining reactions and electrophoretic mobilities; in addition, previous studies of synovial fluid mucin had indicated that the chief polysaccharide is hyaluronate.

Paper electrophoresis of the umbilical cord extracts at the same pH resulted in a pattern with four components. The first three were identical in all respects with those described above. The fourth (Fraction D) did not stain with brom-

Paper Electrophoresis of Mucin

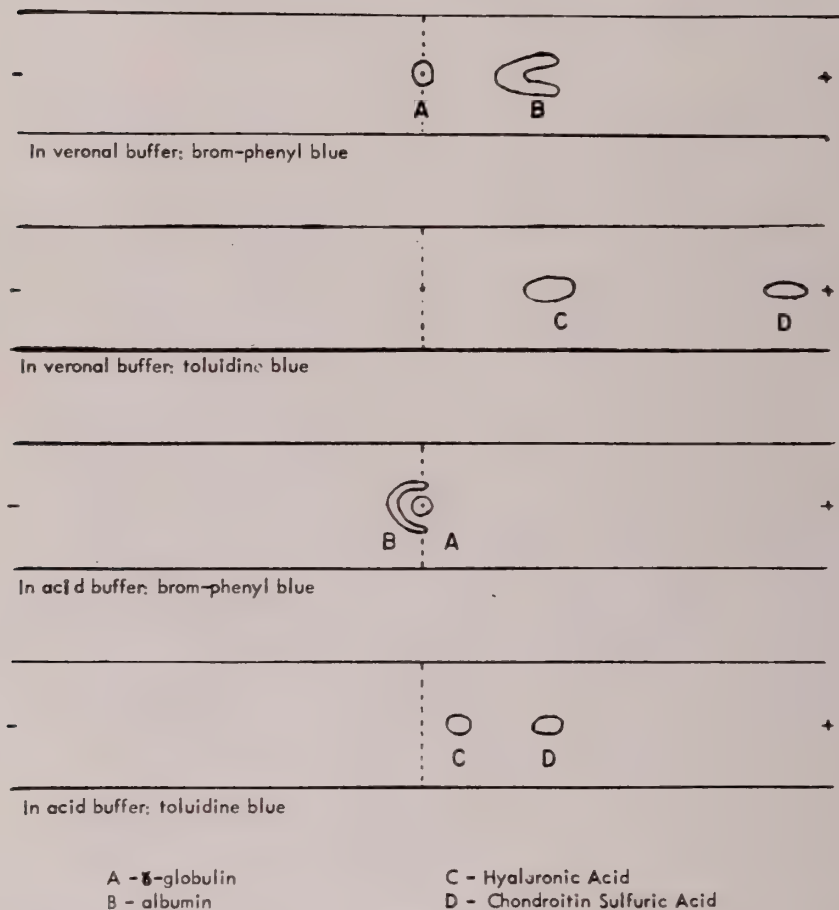


FIG. I

1. In veronal buffer (pH 8.6) all fractions except the globulin move towards the anode. Fractions B and C are invariably juxtaposed, with C lying exactly inside the fork of B. Fraction D occurs only in samples of mucin from umbilical cords.
2. In acid buffer (pH 4.8) dissociation of fractions B and C takes place, with B moving towards the cathode.

phenol blue, and exhibited metachromasia when stained with toluidine blue (Fig. I). It moved towards the anode much more rapidly than Fraction C, behaving like chondroitin sulfuric acid (12).

When the above specimens were examined in acid medium at pH 4.8, fraction A, presumably γ -globulin, still appeared at the point of origin. Fraction B, which in veronal buffer had appeared in a forklike shape, now formed an eye-brow-like pattern on the cathode side of fraction A. The hyaluronic acid fraction (C) appeared to have moved only a very short way towards the anode. Again all four kinds of mucin, obtained from synovial fluid and from umbilical cords by two methods each, showed similar electrophoretic patterns, although

in acid buffer the residue from the filtration of synovial fluid showed a less marked separation between the fractions.

Electrophoresis in veronal buffer of the products resulting from digestion with hyaluronidase showed one spot at the origin (A), and, at the end of a streak, a small spot which stained both with brom-phenol blue and with toluidine blue. No forking was observed, nor was any metachromasia seen. The same substance in acid buffer demonstrated only one spot at the origin; the "eyebrow" associated with the undigested material was not present, and no metachromasia was detectable. The pattern obtained from the digestion product of mucin with trypsin was very similar. The same also applies to the patterns obtained from the products of double digestion, using hyaluronidase and trypsin in both orders of sequence; it appeared, however, that the acid precipitated mucin gave a smaller spot at the far end of the streak than the material obtained by filtration.

Serum albumin added to any of the undigested mucin preparations invariably moved with fraction B under all experimental conditions and noticeably intensified the "fork" or "eyebrow" portion of the pattern, depending on the buffer used.

DISCUSSION

The problem of the relationship between polysaccharide and protein in synovial fluid mucin has been a disturbing one. Earlier workers, particularly K. Meyer (13), have maintained that hyaluronic acid occurred as a free polysaccharide and that the mucin clot is an artefact. However, as Ropes et al. (1) have pointed out, solutions of hyaluronate alone do not display the properties observed in native synovial fluid, suggesting that the protein-polysaccharide complex is not appreciably dissociated under physiological conditions.

Ogston and Stanier (2, 3) have drawn attention to the fact that the slightest degradation of the mucin complex results in a significant loss of viscosity; they feel that synovial fluid mucin in its native state is a hyaluronate-protein complex. Our studies did not attempt to elucidate this particular aspect of the problem, but in working with these materials the impression is obtained that the polysaccharide and the protein are intimately related. The mere fact that isolation of mucin from different sources results in products which are strikingly similar in physical properties and chemical composition and have identical electrophoretic patterns, tends to confirm this idea.

In our initial efforts to characterize the proteins present in the material under investigation, the amino acid content of hydrolysates was determined by means of paper chromatography and other techniques. Since quantitative studies were not done, no specific patterns emerged by means of which these proteins could be differentiated from others.

The experiments using paper electrophoresis confirm the impression of earlier workers that the proteins incorporated in the mucin complex of synovial fluid are an albumin, apparently identical with serum albumin, and another protein which has the mobility of γ -globulin. Similar results were obtained by Hesselvik (14) using the Tiselius electrophoresis apparatus. Ropes et al. also found two

protein components, the faster of which had the mobility of serum albumin. Ogston and Stanier, from the chromatographic analysis of a hydrolysate of the protein fraction of the mucin complex, observed that its amino acid composition was similar to that of serum albumin.

In our studies it has been shown that bovine serum albumin added to synovial fluid mucin and human serum albumin to umbilical cord mucin migrate electrophoretically with protein fraction B under all experimental conditions, and simply reinforce the intensity of the spot. In undigested mucin this fraction invariably appeared partially surrounding the polysaccharide part in the "fork" or "eyebrow" fashion described above. No such pattern has previously been reported. It is our belief that the shape of these patterns is dependent primarily on differences in viscosity between two components of somewhat similar mobilities. If the mucin is applied as a linear streak at right angles to the axis of the paper instead of as a spot, the albumin moves around the hyaluronic acid only at the end of the line, while the middle part of the two components remains in contiguous parallel lines. The hyaluronate zone of the paper was eluted and hydrolysed, and was found to be free of amino acids. This would indicate that under these experimental conditions complete separation of the fractions occurs.

Study of the mucin extracted from umbilical cords produced results of even greater interest. These substances contain two polysaccharides, one identical with the hyaluronate found in synovial fluid, and another faster moving component which has the characteristics reported for chondroitin sulfuric acid (12). The protein fractions appear to be qualitatively identical with those seen in synovial fluid mucin. A relatively stationary component with the properties of γ -globulin, and a fraction with the mobility of serum albumin were again observed. Since the cords were completely freed of blood before extraction, these constituents must therefore have been derived from the tissues themselves. This is of potential significance since it implies that elements of the plasma may be of great importance in the formation of the amorphous ground substance. It has long been suspected that plasma proteins can pass from the intravascular compartment to the extracellular space in the presence of normal capillaries. Recent investigations, particularly those using albumin labeled with radioactive iodine or dyes, indicate that considerable extravasation of this protein from the blood vessels takes place under normal conditions. Thus it appears likely that the protein moiety of the connective tissue ground substance may be derived directly from the plasma proteins in both normal and pathologic circumstances, as suggested by Klemperer (15). These proteins enter the tissues where they may combine with polysaccharides, probably of local origin, to form the amorphous components of the extracellular interfibrillar ground substance.

In those conditions in which abnormal serum proteins are circulating, these too may pass through the capillary wall resulting in the formation of abnormal ground substance. Such a mechanism was postulated to explain the formation of fibrinoid material in connective tissue by Altschuler and Angevine (16). A similar relationship may exist between the pathologic globulins circulating in the blood of patients with multiple myeloma and the deposition of amyloid in

that disease. Thus study of serum proteins in those diseases in which abnormalities of the ground substance have been observed, as in disseminated lupus erythematosus, rheumatic fever and others, may provide valuable information as to their origin and pathogenesis.

SUMMARY

1. Mucin isolated from synovial fluid and umbilical cords was studied by means of paper chromatography and paper electrophoresis.

2. The mucin from both sources was found to contain two protein fractions on electrophoresis: one apparently identical with serum albumin, and another with the characteristics of γ -globulin.

3. The isolation of these proteins from solid, blood-free tissue suggests the possibility that serum proteins play a role in the formation of the interfibrillar ground substance.

ACKNOWLEDGEMENT

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LIVER PATTERNS IN BILIARY HYPERCHOLESTEREMIC XANTHOMATOSIS

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One of the immeasurable advantages of a pathologist in a hospital in which members of the clinical staff have particular interests in unusual conditions is that one has the opportunity to see certain diseases and often many phases of the same disease one might otherwise never encounter. This has been particularly true of the Mt. Sinai Hospital, and I believe that Dr. Klemperer, as Pathologist to this great institution, would be the first to admit that he has had opportunities that are offered to few pathologists. It has been my good fortune to have had the privilege of working with Dr. Thannhauser, whose interest in metabolic diseases covers a period of many years, and through him I have had access to many patients with jaundice, hypercholesteremia and xanthomatosis, and through autopsy and biopsy studies have seen patterns in the liver I had not seen before. Because of Dr. Klemperer's deep interest in metabolic diseases and especially because of his many contributions in the field of liver pathology, it seems appropriate that this paper dealing with both disturbances in metabolism and structural changes in the liver should be written in his honor.

Ever since Addison and Gull (1) in 1851 described a clinical syndrome characterized by long-standing jaundice, a palpably enlarged liver and cutaneous xanthomatosis,—a syndrome which they believed had its seat in the liver, there has been much speculation as to the nature of the pathology in this organ in patients with this condition. In the course of time, subsequent studies by many investigators have shown that this triad of clinical signs and symptoms is commonly associated with hypercholesteremia. This hypercholesteremia, like jaundice, it is believed is dependent upon or related to structural changes within the liver. It is with these changes that this paper is primarily concerned. In seeking a group name to include all cases showing this clinical syndrome, irrespective of the underlying pathology in the liver, the term "biliary hypercholesteremic xanthomatosis" has been suggested. This will serve to distinguish this family of diseases from the primary hypercholesteremic group and from other forms of secondary hypercholesteremic xanthomatosis related to diseases of the pancreas, thyroid or brain. There does not seem to be any justification however for a similar group term to include all forms of liver disease that may be found in patients with biliary hypercholesteremic xanthomatosis since their etiology and pathogenesis have so little in common.

The patterns which one encounters within the liver in this group of patients will of course vary in intensity and extent from case to case, and any of these patterns may be superimposed on pre-existing liver disease just as some terminal and quite unrelated disease such as cancer or tuberculosis may overshadow one

of these existing patterns. Furthermore, it would appear, at least from my own experience, that any one of these liver patterns may be found in the absence of the complete syndrome. This latter observation is, I believe, important, for it would seem that deranged morphology alone is not the only factor that may be involved in the initiation of this particular syndrome.

Biliary hypercholesteremic xanthomatosis is not a common syndrome, and of the eight patterns that are to be described some are seen very rarely.

1. *Pericholangiolitic Biliary Cirrhosis (2) (Chronic Pericholangio-Hepatitis)*

Of all patients showing the complete syndrome, this particular pattern which tends to progress over a period of years is found most often. This pattern is also known as "primary biliary cirrhosis", "hypertrophic biliary cirrhosis", "cholangiotoxic biliary cirrhosis", and possibly some of the lesions described by Hanot and referred to as Hanot's cirrhosis fall into this type. When well established the liver is large, firm, bile stained and finely nodular. The extra-hepatic biliary tract is normal. The specific lesion is an insidious low-grade chronic inflammatory reaction that originates in each of the portal areas at about the same time and extends slowly into the peripheral zones of the lobules (Fig. 1). There is a gradual disappearance throughout the liver of many of the interlobular bile ducts, and bile is retained in small amounts within the lobule. The large bile ducts are not involved in this inflammatory reaction. In the end stage the lobular arrangement of the liver may be so lost and the scarring and nodular reconstruction so complex that, without recourse to earlier biopsies, the histogenesis could remain obscure. It is of interest that in the early stages of this disease there

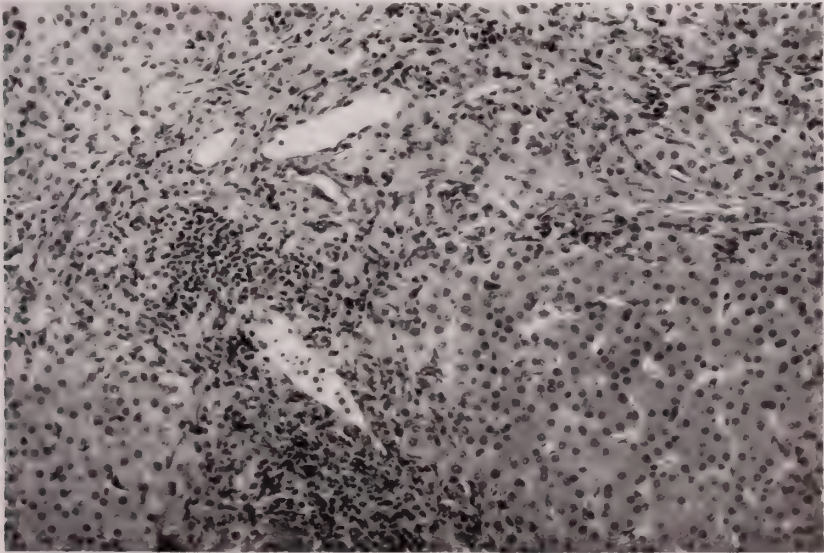


FIG. 1. Portal area from the liver of a patient with pericholangiolitic biliary cirrhosis. There is no interlobular bile duct in the field and cholangioles are difficult to find. There is a chronic inflammatory reaction throughout the area reaching out into the periphery of the bordering lobule.

is not only a striking disproportion between the minimal degree of jaundice and the extraordinarily high levels of blood cholesterol that may be found, but also between the minimal histological changes in the liver and the clinical signs and symptoms. The etiology is unknown, but age and sex would seem to be important factors. An atypical or probably allergic reaction to arsenic has been suggested in isolated cases.

2. *Congenital Acholangic Biliary Cirrhosis (3) (Congenital Absence or Atresia of Interlobular Bile Ducts)*

This of course is a pattern that is only encountered in infants and children and like the others, it may be found with and without cutaneous xanthomatosis. It is very uncommon. In this condition the pattern within the liver is dominated by a partial or complete absence of the interlobular bile ducts from the portal areas. The liver is moderately enlarged and bile stained. The surface may be smooth or very finely granular. Histological studies reveal a variable degree of bile stasis and usually a minimal low-grade chronic inflammatory reaction confined to the portal areas (Fig. 2). This particular anomaly may be found in the presence of a grossly intact extrahepatic biliary system in which each of the large hepatic ducts may be traced for a short distance into the substance of the liver. This fact is important since the underlying disease in the liver can easily be overlooked at the autopsy table.

3. *Acquired Absence of Interlobular Bile Ducts*

This must be distinguished from the congenital form described above, as a condition appearing in adults who for years have shown no evidence of liver

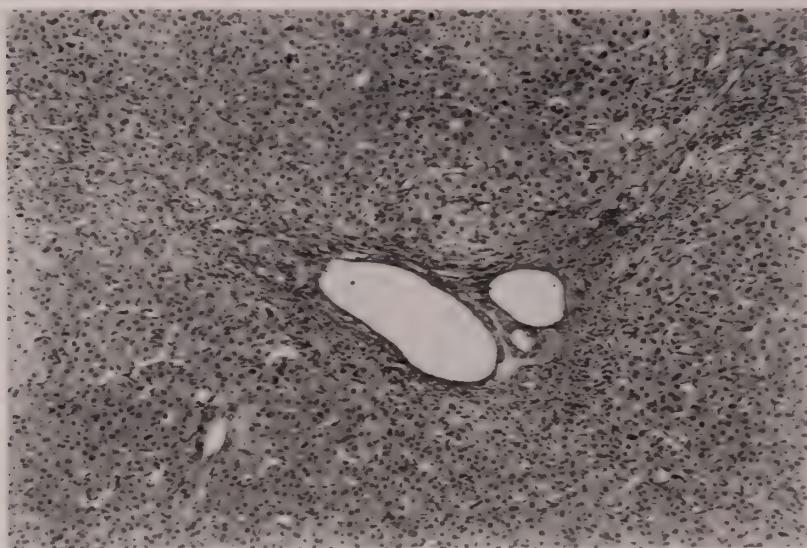


FIG. 2. Liver, from a child with acholangic biliary cirrhosis. In this portal area which is accentuated there is a low grade chronic inflammatory reaction. There is no interlobular bile duct, and terminal cholangioles are difficult to find.

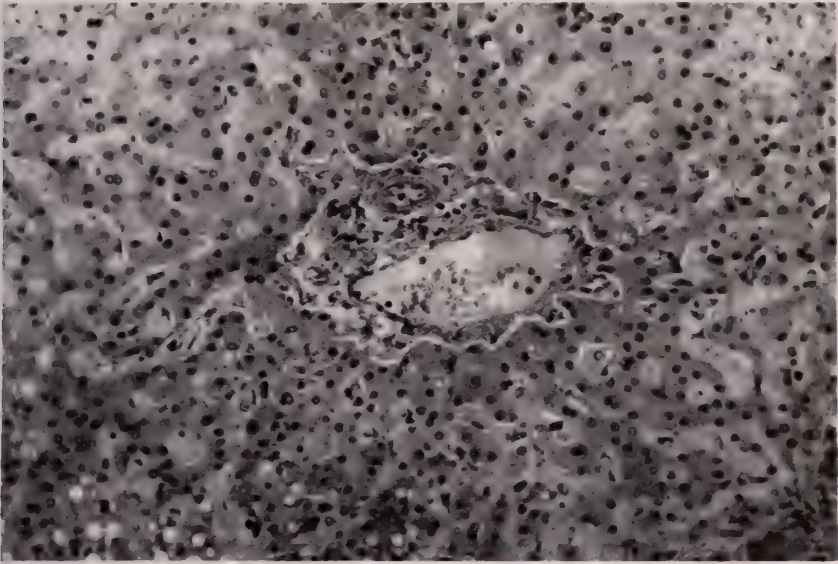


FIG. 3. Liver, from an adult with acquired loss of interlobular bile ducts. This is a portal area showing no interlobular bile duct and no recognizable cholangiole. There is no inflammatory reaction, and the lobular pattern is preserved.

disease. Following a sudden onset, this condition may progress slowly for months and terminate fatally within a year. In the end stage the liver is large, smooth, bile-stained, devoid of every trace of cirrhosis and the extrahepatic biliary tract is free of disease. Microscopic examination reveals a perfectly preserved lobular pattern and well formed portal areas. There is extreme bile stasis, but what is most important, interlobular bile ducts may be absent from 90% of the portal areas. The large bile ducts are unaffected. When seen for the first time in the terminal stages, there is nothing in the portal areas to indicate its pathogenesis. For example, there is no demonstrable inflammatory reaction, there is no scarring or scirrhosis, and one can only postulate that in the earlier stages of the disease there has been an inflammatory reaction with necrosis of bile duct epithelium and this, having been destroyed, has failed to regenerate. In one patient this disease within the liver appeared abruptly following the use of chlorpromazine, a drug which in some cases may have a specific effect on bile duct epithelium.

4. *Obstructive Biliary Cirrhosis (4) (Chronic Biliary Obstruction)*

This is a very common pattern in the liver, and one that is found in both sexes and at all ages, but one that is only very rarely related to hypercholesteremic xanthomatosis. Examples of biliary hypercholesteremic xanthomatosis that have been related to chronic extrahepatic biliary obstruction include occasional cases of carcinoma of the head of the pancreas, inflammatory atresia of the large bile ducts and cases of post-operative ligation of the common duct. The gross and histological findings in uncomplicated obstructive biliary cirrhosis are so

well known that they scarcely bear repeating. The pattern is simply one of an accentuation of the lobular markings by a mild chronic inflammatory reaction in all portal areas. This is associated with an elongation and increase in the number of cholangioles, a dilatation of cholangioles and interlobular bile ducts by retained bile, and intensive centro-lobular bile stasis. This is one form of cirrhosis in which the etiological mechanisms are relatively straight forward and where removal of the cause usually leads to clinical recovery.

5. *Cholangiolitic Biliary Cirrhosis (5) (Chronic Cholangio-Hepatitis)*

Mallory (6) who called this "infectious cirrhosis" in 1911 on the basis of bacteriologic studies he had done, is perhaps more closely identified with this particular pattern in the liver than any other investigator. This pattern is also known as "Non-obstructive cholangitic cirrhosis" or simply as "cholangitic cirrhosis." It is seen less frequently than the uncomplicated obstructive type, and again only a very small number of patients with this disease of the liver will show hypercholesteremic xanthomatosis. While the pattern varies considerably from case to case, the liver is usually large, firm, finely nodular, bile-stained and, with the naked eye, the cut surface is finely scarred. Its most characteristic histological feature is a chronic proliferative inflammatory reaction within the walls and lumina of the small interlobular bile ducts and terminal cholangioles. This is associated with a striking marginal hyperplasia of new cholangioles. This reaction, often asymmetrical in respect to the portal area, spreads out in a fan-like manner into the adjacent lobules. There is usually bile stasis within the lobules. When well established, the portal areas are lengthened and widened and communicate with one another to form rings of inflammatory connective tissue isolating each lobule. The striking inflammatory hyperplasia of cholangioles, the immediate involvement of the lumina and walls of small bile ducts in the inflammatory process and the persistence of most of the interlobular ducts tend to distinguish this pattern from the low-grade slow smouldering progressive reaction seen in pericholangiolitic biliary cirrhosis. The etiology may be viral, bacterial or chemical. A similar pattern has been seen in the livers of infants with toxoplasma infection and in very young children with "fibrocystic disease of the pancreas". When bacteria are the cause, partial obstruction of the common duct, even though only temporary, would seem to play an important predisposing role.

6. *Pigment Cirrhosis (7)*

Hemosiderosis of the liver with or without hemochromatosis, with scarring and nodular reconstruction is one of the simplest types of cirrhosis to identify grossly or histologically. It is not an unusual disease but its association with jaundice and hypercholesteremic xanthomatosis has only rarely been recorded. While its advanced pattern is well known, it is not as generally recognized that in its early stages the structural pattern has many features in common with biliary cirrhosis. The loss of liver cells and the replacement by fibrous tissue usually begins at the outermost portion of the lobule, leading to a widening and

lengthening of portal areas, an interruption and compression of cholangioles and at times intralobular bile stasis. A proliferation of new cholangioles is usually a conspicuous feature. This process may continue for some time before there is a loss of the normal lobular pattern.

7. *Post-hepatic Cirrhosis (8)*

In comparison to the frequency with which one encounters this disease in the liver, biliary hypercholesteremic xanthomatosis is a rare condition. A pattern very closely resembling that of pericholangiolitic biliary cirrhosis has occasionally been found following viral infections of the liver and a history of repeated arsphenamine injections. This particular pattern is characterized by scarring in the portal areas which extends out into the periphery of the lobules, a variable degree of bile stasis, a disappearance of many of the smaller interlobular bile ducts and a nodular reconstruction of the parenchyma. Unlike the classical pattern of pericholangiolitic biliary cirrhosis in which the normal lobular pattern is long preserved, the pattern in this form of post-hepatic cirrhosis is one of a replacement of normal lobules by small nodules of regenerated liver cells. This form of cirrhosis is not commonly found in patients with biliary hypercholesteremic xanthomatosis, yet it is important that one should recognize it since cases are on record as having shown a complete remission of the syndrome.

8. *Fibro-xanthomatous Biliary Cirrhosis (9)*

In three patients, all young children with skeletal and cutaneous xanthomatosis, but with cholesterol blood levels within normal limits such as may be found

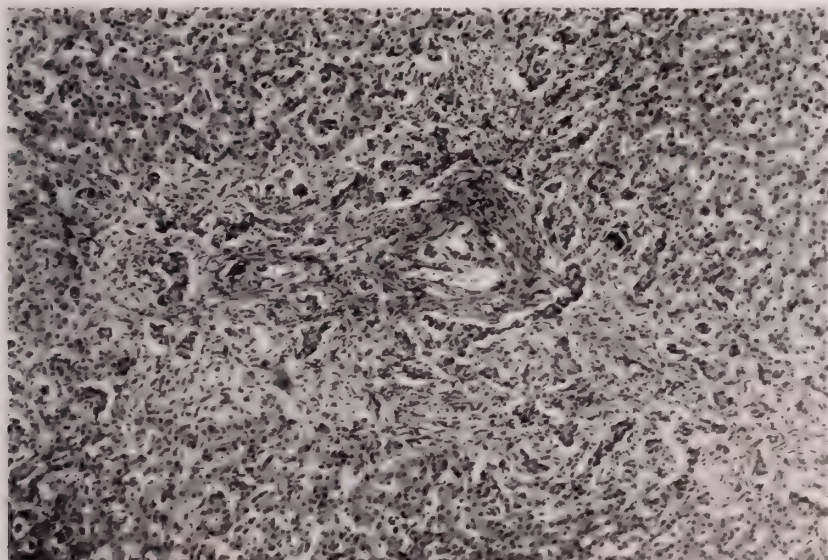


FIG. 4. Liver, from a child with fibroxanthomatous biliary cirrhosis. The portal area shown in this field is accentuated by a proliferation of lipid laden histiocytes, fibroblasts and a light lymphocytic infiltration.

in the Hand-Schuller-Christian syndrome, there appeared after months of careful observation a mild degree of jaundice, a moderate elevation in the blood cholesterol and a palpably enlarged liver. In each case the disease terminated fatally. At autopsy the liver was large, firm, bile-stained and finely granular. The extrahepatic biliary tract was healthy, and the common duct was patent. Microscopic sections of the liver revealed a type of biliary cirrhosis characterized by fibroxanthomatosis of all of the portal areas. This was a uniform process leading to compression and destruction of interlobular bile ducts. The lobular pattern was preserved, and the lobules were bile stained. This change throughout the portal areas was simply part of a diffuse process involving to a variable degree almost every organ in the body. Because of the distinctly fibroxanthomatous character of the portal areas, the descriptive term of "fibroxanthomatous biliary cirrhosis" was suggested. It is important to emphasize again that the xanthomatosis in these children long preceded either the hypercholesteremia or the jaundice. This strongly suggests that here the fibroxanthomatosis throughout the liver was not only responsible for the bile stasis but was also the mechanism causing the late elevation in cholesterol.

DISCUSSION

A sub-title to this paper could have been "biliary hypercholesteremic xanthomatosis, eight distinct diseases of the liver from which this clinical syndrome may arise," for what I have tried to point out is simply, that seeing a patient for the first time with this complete syndrome one has at least eight possibilities in respect to liver patterns to consider. Needless to say, some of these in one's differential diagnosis could be eliminated at once. It may seem at first glance that such a classification, based on morphology alone, would confuse rather than clarify an already complex problem, and yet if one is going to attack this basic metabolic problem, it is important to recognize that at least eight distinct diseases of the liver may initiate this clinical syndrome. There is a more practical aspect to this classification however since therapy and prognosis in each patient will depend on the nature of the particular liver disease in each case.

Before leaving this particular facet of lipid metabolism, I would like to remind the reader again that there are many cases of hypercholesteremia with and without xanthomatosis in which the liver is grossly and histologically normal. However in any of these cases, irrespective of the underlying mechanisms involved, one may find a rare histiocyte or even a minute collection of histiocytes laden with lipid along the sinuses or embedded in the portal connective tissue. Among the unusual and apparently chance findings that we have seen in the liver in patients with hypercholesteremia are three that are worthy of mentioning. The first was a large solitary xanthoma in an otherwise normal liver. The second was a small collection of lipid-laden histiocytes, lymphocytes and fibroblasts building a solitary granuloma in an isolated portal area. The third and last is perhaps the exception that only proves the rule. A middle-aged female, who had been followed for years as a classical example of primary hypercholesteremic xanthomatosis, began developing a mild jaundice and an enlarging

liver. Biopsies at this time and one year later showed the histological pattern of progressive pericholangiolitic biliary cirrhosis.

SUMMARY

The term biliary hypercholesteremic xanthomatosis has been suggested to include all patients showing the syndrome of jaundice, enlarged liver, hypercholesteremia and xanthomatosis. This appears to be a clinical syndrome dependent on a variety of different diseases of the liver, any one of which may be found in the absence of the complete clinical syndrome. Eight different diseases of the liver have been seen and described in patients of all ages showing this syndrome. Of these eight patterns, the one most commonly related to Biliary hypercholesteremic xanthomatosis has been chronic pericholangiolitic biliary cirrhosis.

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THE ROENTGEN FINDINGS IN LYMPHOSARCOMA OF THE SMALL INTESTINE

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INTRODUCTION

Early recognition of primary neoplasms of the small intestine is difficult due to the paucity of localizing symptoms and signs relating to the disease until it is far advanced. This is particularly true of primary lymphosarcoma of the small intestine because obstruction is infrequent. This is in contrast to carcinomas in this region, where obstruction is often the first presenting symptom. The most useful diagnostic aid is roentgen study of the small bowel. With increasing experience with small intestinal lymphosarcomas as well as the recognition of the abnormal patterns produced by other small intestinal ailments, it has become apparent that primary lymphosarcoma of the small bowel often presents an appearance which is highly suggestive of the underlying pathological alterations. It is true that lymphosarcoma of the small bowel may present in a variety of forms which, at first glance, may seem to bear little relation to each other. It will be seen, however, that the differences in the roentgen changes produced are primarily a function of the direction of growth and multiplicity of lesions. A classification of these roentgen changes, therefore, is of practical usefulness.

The purpose of this paper is to present the roentgen findings in a series of 62 proven cases of primary lymphosarcoma of the small intestine. They may be classified as follows:

1. Predominantly invasion of the mesentery
 - a. large extraluminal masses (single or multiple with extrinsic pressure upon the small intestine)
 - b. production of the sprue pattern
2. Polypoid form (intussusception)
3. Infiltrating form
4. Multiple small nodular defects
5. Endo-exo-enteric form with extensive excavation, perforation and fistula formation.

GENERAL CONSIDERATIONS

The frequency of lymphosarcoma in the various portions of the small intestine parallels roughly the distribution of lymphoid tissue within the small bowel.

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Accordingly, it is more common in the ileum where larger lymphoid collections (Peyer's patches) exist.

The tumor may arise in the lymphoid tissue of the mucosa or sub-mucosa. It has a tendency to extend along the long axis of the bowel and may take origin from multiple sites. This is in contrast to the usual behaviour of carcinomas in this region which produce a single short segmental constricting lesion.

In the initial stages, lymphosarcoma may appear as a discrete, thickened, nonulcerated plaque with relatively intact overlying mucosa. Presumably, if it arises superficially, that is, in the mucosa, growth may be predominantly towards the lumen causing no remarkable rigidity in the adjacent bowel wall. As a result, exaggerated peristalsis, occasioned by the intraluminal mass, may attempt to expell the mass and produce an intussusception with subsequent intestinal obstruction.

Lymphosarcoma, however, may extend intramurally, causing a diffuse thickening of the wall of the small intestine over a considerable distance. When this occurs in the submucosa, the folds of the mucosa may appear intact. Sometimes they may be smoothed out by the submucosal thickening and on occasion, may even appear coarsely thickened. When the infiltration is more superficially located, the overlying mucosa may be thrown up into innumerable small polypoid projections. This diffusely infiltrating form is not associated with any single mass, but, along the course of the involved bowel, alternating areas of greater and lesser involvement may be found producing a grossly irregular, rigid, unchanging appearance.

In contrast to this type of extension, that is, along the longitudinal axis of the bowel, growth may occur essentially outwards. In this situation the mass is usually large and both endo- and exo-intestinal in position. As the mass grows, it destroys the intestinal wall and extends into the mesentery, infiltrating and destroying adjacent intestinal loops. Ulceration of the tumor occurs with the formation of many intercommunicating channels within the tumor mass as well as into the adjoining involved bowel loops. Ulceration and necrosis within the tumor continue producing a large irregular excavation which communicates with several loops of bowel. Performations that occur, therefore, are rarely into the free peritoneal cavity but rather into the agglutinated mass of tumor, mesentery and small intestine.

Lymphosarcoma is a medullary tumor and as such does not evoke a desmoplastic response. As a result, there is little tendency for scirrhus tissue to form and for stenosis to occur. A certain degree of narrowing of the bowel lumen may occur as a result of extrinsic compression and marked thickening of the bowel wall, but stricture formation of sufficient severity to cause intestinal obstruction is rare. When it occurs, it is associated with ulceration and secondary infection. In one instance, in the present series, the ulceration which had evoked mechanical intestinal obstruction by producing marked spasm, was not located in the tumor itself but immediately adjacent to it. This situation is extremely rare. Intestinal obstruction in lymphosarcoma is most often incident to intussusception.

In some cases, the infiltrated bowel wall reveals a remarkable local segmental dilatation, sometimes of "aneurysmal" character. The apparent atonicity has been explained as the result of destruction of the muscular coat by the tumor as well as involvement of the nerve plexuses.

Diffuse involvement of the mesentery by extraluminal extension of lymphosarcoma may produce alterations in absorption of nutrients from the intestinal tract. Fats, being the most difficult substances to absorb, are generally the first to be affected and steatorrhea may result. The clinical and laboratory findings may then be indistinguishable from those seen in idiopathic sprue. However, failure to respond to the usual therapy of idiopathic sprue or the subsequent development of other evidences of lymphosarcoma lead eventually to the correct diagnosis.

ROENTGEN FINDINGS

1. Predominantly Invasion of the Mesentery

a. Large extraluminal masses. The greater portion of the tumor may grow centrifugally and produce large extraluminal masses which can attain huge proportions and even extend into the retroperitoneum. They manifest themselves radiologically by displacement of the abdominal organs, pressure defects upon adjacent viscera and invasion of the intestinal wall. The presence of a mass alone is not diagnostic of lymphosarcoma unless mural alterations are seen in the small intestine which characterize this type of growth.

It is again of interest to note that in this form of lymphosarcoma, intestinal obstruction does not occur. In metastatic carcinoma, however, in which there is involvement of the mesentery and infiltration of the bowel, incomplete obstruction is not uncommon.

b. Production of the sprue pattern. Along with the clinical and laboratory findings of sprue which can be produced when there is diffuse involvement of the mesentery, a roentgen picture simulating sprue also may be found (Fig. 1). Eight such cases have been observed in this series. In six, the sprue pattern was seen with dilatation of the small intestinal loops, hypersecretion and segmentation of the barium column. The findings were indistinguishable from those seen in idiopathic sprue and a definite roentgen diagnosis of lymphosarcoma could not be made. In two additional cases, there was evidence of extraluminal masses with displacement and invasion of the small bowel loops superimposed upon the sprue pattern.

In our experience, three diseases most commonly may produce the sprue pattern on roentgen study. These are idiopathic sprue, lymphosarcoma and Whipple's disease. They do not, however, invariably produce the sprue pattern on roentgen study.

2. Polypoid Form

When the tumor has grown to a size sufficient to produce a discrete intraluminal mass and is without intramural extension, it may be drawn forward by peristalsis, forming a pseudopedicle, and become the leadpoint of an intussus-



FIG. 1. Diffuse lymphosarcoma of the mesentery and retroperitoneum, mimicking the sprue pattern, manifested by segmentation, hypersecretion and flocculation of the barium column. There is no evidence of intrinsic involvement of the bowel wall.

ception (Figs. 2, 3). Unless there are other clues to the nature of the underlying lesion, the cause of the intussusception cannot be determined from the roentgenograms. The polypoid tumor itself is rarely visualized on roentgen study because it is prone to intussusception and may become obscured by the intussusceptum and intussusciptions.

Four times in this series, intussusception only was seen. In two others, marked thickening of the mucosal folds in the region of the intussusception with fistulas

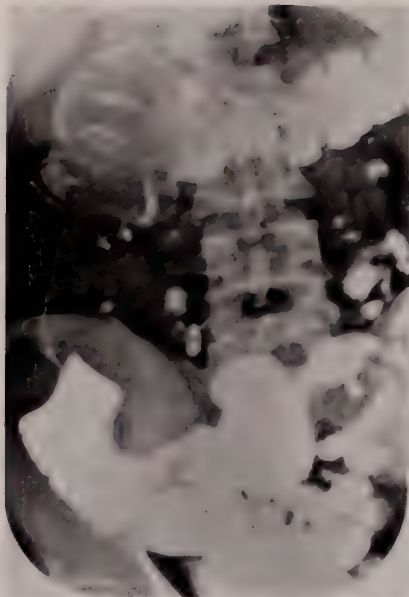


FIG. 2

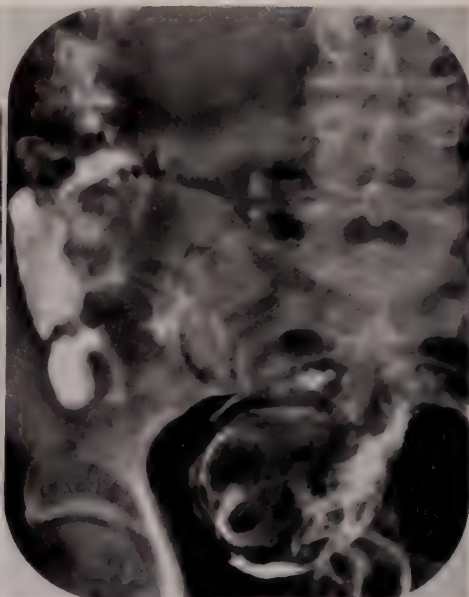


FIG. 3

FIG. 2. Polypoid lymphosarcoma of the terminal ileum resulting in an ileocolic intussusception with minimal obstruction. The lesion in the ileum is obscured by the intussusceptum.

FIG. 3. Large lobulated polypoid lymphosarcoma of the terminal ileum seen after evacuation of a barium enema.

and nodularity of the adjacent mucosa were noted. In one other case, there were multiple polypoid lesions in the small intestine with several areas of intussusception producing a most disorganized small intestinal picture.

3. *Infiltrating Form*

The bowel wall may become diffusely infiltrated by lymphosarcoma and thickened for considerable lengths. The degree of thickening may vary from area to area producing irregular segments of narrowing and relative dilatation. The degree of narrowing is never as marked as that observed in carcinoma or inflammations at this site. The mucosal folds may be flattened, effaced or they may be thickened and thrown up into irregular nodular projections producing coarse, irregular scalloping of the bowel contours with varying sized intraluminal filling defects. The mural thickening causes separation and straightening of the bowel loops which stand out clearly from the usual closely approximated normal small intestinal loops. (Fig. 4). The barium may have a mottled appearance due to increased secretions within the lumen of the affected segment.

The infiltration may be limited to short segments, either single or multiple, which appear as short areas of eccentric narrowing of the bowel lumen with effacement or thickening of the mucosal folds and evidence of tumor formation (Fig. 6). Marked rigidity of the involved segment is not seen nor is there sufficient stenosis to produce dilatation of the small intestine proximally.



FIG. 4

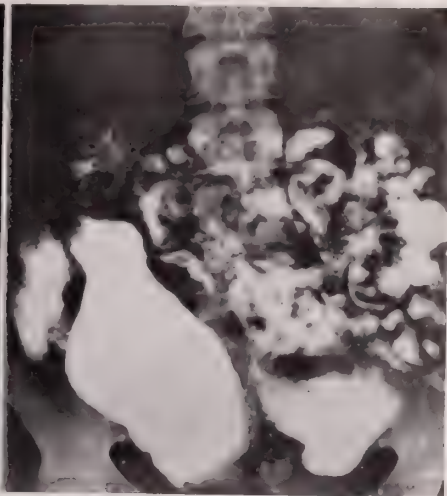


FIG. 5

FIG. 4. Diffuse infiltrating lymphosarcoma of the jejunum and ileum. The intestinal loops are straightened. In some segments the lumen is dilated with scalloped or saw-tooth contours. The wide separation of the loops is due to thickening of the bowel wall by tumor infiltration.

FIG. 5. Infiltrating form of lymphosarcoma of the terminal ileum with "aneurysmal" dilatation. The increased thickness of the bowel wall is indicated by the increase in the soft tissues intervening between the dilated segment and adjacent small intestinal loops.

Associated with this segmental lesion, very small nodular defects along the contours of the bowel lumen are frequently found. They may be situated at some distance from the more conspicuous lesion. They may be single or multiple and are generally less than a centimeter in diameter. They may widen the normal interval between valvuli but do not extend across the full width of the bowel lumen.

Another form of segmental infiltration of the bowel wall in lymphosarcoma is that which extends for fairly short distances and is accompanied by marked localized dilatation. This has been termed aneurysmal dilatation (Fig. 5). The increased thickness of the bowel wall is demonstrated by its separation from adjacent loops. The barium tends to pool within the widened lumen and no mucosal pattern can be seen. The contours of the lumen may be smooth or exhibit a coarse irregularity which may be further enhanced by increased secretions. The adjacent mucosa may appear intact or show evidence of thickening and nodularity.

4. Multiple Small Nodular Defects

These appear radiologically as multiple pea-sized intraluminal nodules which alter the mucosal pattern of the bowel and produce an irregular coarse scalloping of the bowel contours. The bowel lumen may be of normal caliber or increased. It is not narrowed. These changes are usually found in the ileum and involve segments varying from one to two feet in length. The involved segment retains its pliability and is not fixed in position (Fig. 7).

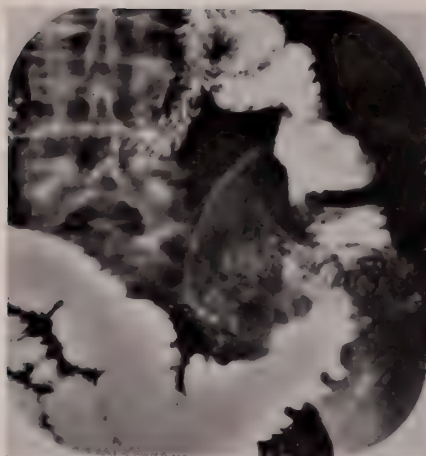


FIG. 6

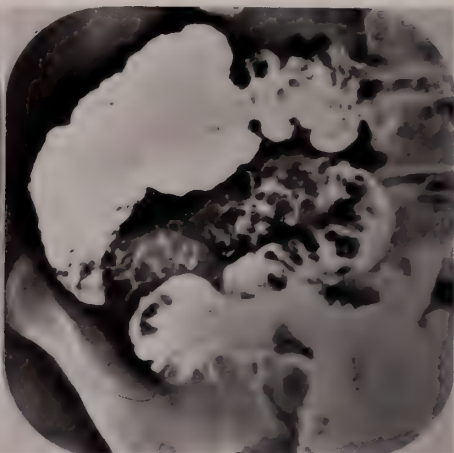


FIG. 7

FIG. 6. Infiltration of multiple short segments of the jejunum by lymphosarcoma. In this case, two areas are involved. The proximal area of involvement shows a segmental area of irregular dilatation of the bowel lumen, destroyed mucosal folds and a suggestion of an intramural mass. The second lesion, a few inches caudad, is manifested by flattening and rigidity of one wall of the bowel with coarsening of the valvular markings on the opposite contour of the bowel lumen.

FIG. 7. Lymphosarcoma presenting as multiple nodular defects in the terminal ileum. The mucosal pattern is replaced by numerous polypoid intraluminal projections which alter the contour and caliber of the bowel lumen.

This form may occur as the sole manifestation of the disease or be associated with other small intestinal changes. We have observed five such cases. In three, the colon was also involved. The colonic changes are similarly nodular and may simulate the roentgen alterations seen in familial polyposis. The changes in the colon may not be seen as easily as in the small intestine because the lumen of the colon is large and distensible and the tiny nodular defects may be obscured by the larger amounts of barium utilized in studying it. In one case, the stomach appeared to be involved independently of the small intestinal lesion.

5. *Endo-Exo-Enteric Form with Excavation*

In this instance, a large excavated mass with multiple fistulas and communications with the adjacent small bowel are seen.

The roentgen findings produced are usually bizarre. The characteristic finding is an extensive irregular amorphous patch of barium which does not conform to the lumen of any portion of the gastrointestinal tract and communicates with the surrounding small intestinal loops. The adjacent small intestinal loops are displaced by the large mass (Fig. 9). Fistulas may be seen within the conglomerate mass of shadows.

The earlier changes are seen less frequently. Before massive excavation occurs, the tumor and involved small intestine may be criss-crossed by many intercommunicating channels connecting the tumor with the lumen of the small intestine. These channels appear as amorphous barium streaks of varying caliber. In one such case, because of the presence of the altered intestinal loops and

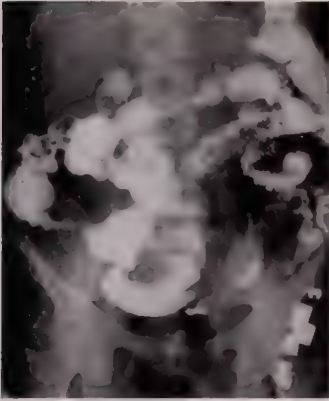


FIG. 8

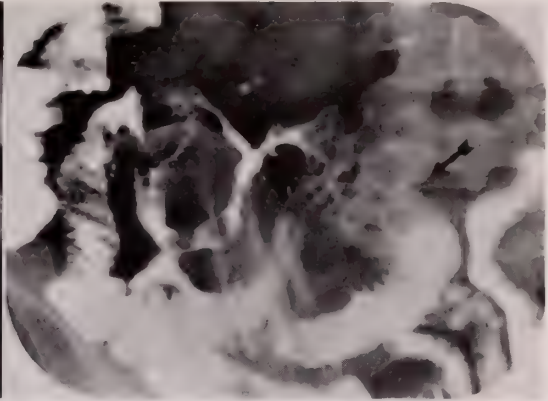


FIG. 9

FIG. 8. Endo-exo-enteric form of lymphosarcoma of the distal ileum with a large irregular triangular excavated area within the tumor containing an amorphous collection of barium. The mucosal folds in the adjacent small intestinal loops are considerably thickened.

FIG. 9. Endo-exo-enteric lymphosarcoma of the distal ileum. The normal bowel lumen is replaced by many intercommunicating tortuous tracts through the tumor. The arrow points to the nodular mucosal pattern proximal to the mass. The lumen of this segment is not narrowed.

fistulas, the diagnosis of regional enteritis was made (Fig. 8). Subsequent events leading to massive excavation of the involved area indicated the nature of the changes observed.

This appearance is not pathognomonic of lymphosarcoma but has been observed in other sarcomatous tumors of the intestinal tract.

HODGKIN'S DISEASE

In general, Hodgkin's disease produces the same kinds of lesions in the small intestine as other forms of malignant lymphomas; however, perforation, fistulas and aneurysmal dilatation have not been as common.

Differing from lymphosarcoma, Hodgkin's disease can produce marked fibrosis of the bowel wall with constriction of the lumen (Fig. 10). Radiologically, there is eccentric narrowing of the bowel lumen which tapers in a fusiform manner. There are no overhanging edges at the margins of the lesion which is usually longer than that seen in carcinoma. The contours of the bowel lumen are irregular due to nodularity of the bowel wall. The involved segment may be fairly long.

The sprue pattern, multiple small nodular defects and the infiltrating forms have all been seen in Hodgkin's disease.

We have seen a single case of leukemic infiltration of the small intestine which appeared as multiple small nodular defects within a short small intestinal loop.

DIFFERENTIAL DIAGNOSIS

1. Multiple polyps in the small intestine: These are rare. When seen, they are usually one of the manifestations of Jaegers syndrome.
2. Infarction of the small intestine: An infarcted bowel segment shows pro-



FIG. 10. Hodgkin's disease of the jejunum. There is a narrow rigid segment producing obstruction to the barium column and dilatation. The contours are scalloped. No overhanging margins are seen. There is a fairly gradual transition between normal and abnormal bowel.

gressive changes initially, proceeding to stricture formation. The findings are similar to a benign stricture in other portions of the gastrointestinal tract, namely, a rigid, stenotic segment with a concentric lumen, the margins of which gradually widen to the caliber of the normal adjacent bowel. The margins are exquisitely smooth. Dilatation of the small intestine proximally occurs.

3. Carcinoma: These lesions are more common in the jejunum. They are usually short, have an eccentric rigid lumen, the mucosa of which shows destruction and occasionally ulceration. The margins of the lesion are overhanging. An extraluminal mass may be present. The lesions are usually single.

4. Carcinoids: Carcinoids occur more frequently in distal ileum than in other regions of the small intestine. They may have the same general appearance as carcinomas. On rare occasion, they may appear as multiple nodular filling defects with some dilatation of the bowel lumen.

5. Regional Enteritis: Two-thirds of these cases involve the distal ileum. The inflammatory process is characterized by fairly long (from 6-8 inches to the entire small intestine) segments of involvement which show destroyed mucosal

ulcerations, inflammatory polyp formation, fistulas, sinus tracts, separation of bowel loops due to thickening of the bowel wall and intervening mesentery, skip areas, spasm, irritability and hypersecretion.

SUMMARY

1. The roentgen findings in 62 cases of primary lymphosarcoma of the small intestine have been described.
2. Because of their varied appearances, a classification based on the predominant pathological changes has been presented.

SYMMETRICAL HEMORRHAGIC NECROSIS OF ADRENAL GLANDS COMPLICATING CORONARY THROMBOSIS

CASE REPORT WITH DISCUSSION OF POSSIBLE ROLE OF CORTICOTROPIN AND HEPARIN

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As a syndrome meriting clinical alertness spontaneous adrenal hemorrhage in adult patients has won increasing attention in recent years. The most frequent complaint listed in the reported cases was pain in the abdomen occasionally generalized but most often epigastric or confined to the lumbar or costovertebral areas (1). Tenderness and spasm were frequent at the site of pain. With progress of the disease pallor, prostration, drop in blood pressure, cyanosis, nausea and vomiting, and finally shock developed. Fever and leukocytosis were frequent findings. In contrast to the classic Waterhouse-Friderichsen syndrome, purpura was usually absent.

The adrenals are among the most vascular organs in the body. As shown by Anson (2), each adrenal is supplied by as many as 50 arteries. Arterial embolism or thrombosis as a general cause of massive adrenal necrosis is therefore unlikely. On the other hand the single vein which drains the adrenal makes it particularly vulnerable to hemorrhagic necrosis in the event of venous thrombosis, as suggested in several case reports (3). While this explanation may be acceptable in instances of unilateral hemorrhagic necrosis, it is less convincing when the lesion is bilateral, as occurs in the majority of instances. The possibility must in fact be considered that venous thrombosis, when demonstrated, may be a complication of hemorrhagic necrosis of the gland and thereby reflect merely incidental injury of the vein as an accompaniment of the parenchymal changes.

Several years ago Rich (4) drew attention to a peculiar type of adrenal cortical damage in acute infections which, when extensive, is commonly accompanied by peripheral circulatory collapse. When the lesion is well developed the normally solid cords of the zona fasciculata (and, to a lesser degree, of the zona glomerulosa) are transformed into hollow structures resembling renal tubules, which may contain coagulated protein, fibrin, polymorphonuclear leukocytes, necrotic cortical cells, or may be empty. The lining cells are often flattened, shrunken, and low in lipoid. According to Rich the earliest stages consist in focal necrosis of isolated cells which are then resorbed and replaced by fluid which dissects the cords into two rows of cells, sometimes for their entire length. The lesion may be focal or involve the entire cortex bilaterally and accompanies severe bacterial infections. More recently Wilbur and Rich (5) were able to duplicate the lesion in rats by administration of very large doses of corticotropin. The role of the anterior pituitary in the pathogenesis of the adrenal necrosis which follows injections of diphtheria toxin was mentioned by Plaut who cited

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Boguth's observation that adrenal necrosis in such instances can be prevented by prior hypophysectomy (6).

Changes in the adrenal cortex under the influence of exogenous corticotropin have been reported by a number of clinical observers. In a case described by Sokoloff and his associates (7), a considerable proportion of the cells, "perhaps ten per cent", revealed degenerative changes. These changes were most marked in the innermost parts of the cortex, principally in the fascicular zone. O'Donnell and his associates (8) suggested that adrenal changes in cases of this type may actually represent the synergistic effect of exogenous and endogenous ACTH.

These considerations provide the theoretical basis for advising caution in giving large doses of corticotropin for treatment of conditions associated with extreme grades of stress. As a possible example of the risk of corticotropin in such conditions the case reported by Wilson and Roth (9) may be cited. This concerned a 51 year old female patient in whom bilateral adrenal apoplexy occurred at the end of three weeks of corticotropin therapy for ulcerative colitis. These authors also cited the earlier paper of Rich in support of the view that actual apoplexy is merely a sequel to other severe degenerative changes in the adrenal cortex due to stress. Greene (10) reported a case of bilateral adrenal hemorrhage in a man of 60 with arthritis and hypertension in whom 525 mgm. of corticotropin had been administered in a period of five days.

The following case is reported as an example of symmetrical hemorrhagic necrosis of the adrenals occurring in a case of myocardial infarction with circulatory collapse wherein corticotropin was given in an effort to check intestinal bleeding which complicated the use of heparin:

CASE REPORT

F. W. B., 52, male, was admitted to the Middlesex General Hospital May 8, 1955 with history of sudden onset of severe chest pain located over the precordium and radiating to the right shoulder. The pain was more or less continuous and associated with a sense of tightness and soreness and a profuse sweat. Pain was worse on deep inspiration and prevented the patient from taking a full breath. On his admission the following morning his pain was somewhat less but sweating was still profuse. A few fine rales were heard at the lung bases. Cardiac rhythm, which had been somewhat irregular, was now regular, and the heart sounds, which had been distant and feeble, had become more distinct. Blood pressure was 140/120 mm. Hg. The extremities were warm. The clinical impression was coronary arterial thrombosis. Hemoglobin was 17.0 gm. per cent; RBC, 5,040,000 per cu. mm.; WBC, 16,800 per cu. mm. with a normal differential count. During that day the blood pressure dropped to 70/50 mm. Hg but was restored to 112/76 mm. Hg after injections of Wyamine®. The patient still had dull aching pain and sense of pressure in the chest and continued to sweat profusely. ECG revealed findings compatible with posterior and posterolateral myocardial infarction, confirmed in serial tracings. The latter also revealed frequent ventricular premature beats which at times produced coupled rhythm.

The patient's subsequent clinical course was marked by dyspnea, orthopnea, basal rales, and considerable instability in blood pressure which at times dropped to as low as 60/50 mm. Hg and averaged about 104/70 mm. Hg, requiring frequent support with Wyamine®. Anticoagulant therapy was administered after the first day in the form of intramuscular heparin (50 mgm., preceded by hyaluronidase at the injection site, every four hours). The patient was digitalized. Quinidine was also given to control the arrhythmia. Pain persisted

and was attributed to complicating pericarditis, which was now recognized by a loud friction rub over the entire precordium.

About one week after admission his general condition seemed slightly better. He still had chest pain and complained at times also of upper abdominal pain with some distention. His face seemed grayish and he sweated profusely, yet his blood pressure was maintained at 130/100 mm. Hg without vasopressor agents. The possibility was suggested that the abdominal pain was referred pain related to pericarditis, but mesenteric embolism could not be excluded nor, because of the relative elevation of blood pressure, embolism of the renal artery ("Goldblatt kidney"). Because of these possibilities it was decided to increase the dose of heparin to 75 mgm. every four hours. After the second injection of heparin in the higher dosage the patient had bloody diarrhea and appeared to be much worse. His blood pressure dropped to 82/60 mm. Hg. He was given Wyamine[®], adrenochrome, and a whole blood transfusion. Mesenteric embolism was suspected as the cause of the bloody diarrhea but the possibility that it might have been due to heparin was also considered and heparin was therefore temporarily stopped and protamine sulfate (5 cc.) was administered intravenously. It was noted however that throughout the period of heparin therapy clotting time had averaged about 14 minutes (Lee-White) and was often less, yet following interruption of heparin it rose to 44 minutes. The possibility of hidden purpura due to quinidine was also considered and quinidine was also stopped. However, no platelet count was made. As an added measure to control hemorrhage corticotropin was begun on the eleventh hospital day and its administration was continued at a dosage level of 20 mgm. every 12 hours for three days and 15 mgm. every 12 hours for another three days, totalling 210 mgm. in six days. These measures appeared to be successful in controlling bleeding and it was felt that with the greater risk of recurrent thromboembolism as a result of abrupt withdrawal of heparin it would be desirable to resume heparin promptly. The latter was begun again on the twelfth hospital day in a dosage of 50 mgm. intravenously every 12 hours. The clotting time from now on ranged between 10 and 20 minutes.

Two days after resumption of heparin and while still receiving corticotropin the patient again had abdominal cramps and considerable tenderness in the left costovertebral angle. He complained of frequent dizziness but his blood pressure remained at a level of about 110/80 mm. Hg. The possibility of pyelitis or renal infarction was considered. However, his general condition seemed better and the abdomen became soft and nontender. He was now running a more or less continuous low grade fever and became somewhat disoriented. He developed more abdominal distention and increasing costovertebral angle tenderness bilaterally but his urine remained essentially clear. The diagnostic possibilities were now extended to include retroperitoneal suppuration or acute pancreatitis. He was found to have mild azotemia (NPN, 66 mgm. per cent; creatinin, 2.85 mgm. per cent) and normal serum amylase.

On the twenty second hospital day he developed sudden pain in the right calf with coolness and blanching of the foot and other evidence of acute embolism of the right popliteal artery, presumably secondary to mural thrombus of the infarcted left ventricle. Blood pressure was 104/78 mm. Hg. A surgical consultant recommended femoral embolectomy for possible salvage of the extremity and the patient was prepared for surgery. He was unable to tolerate local anesthesia because of restlessness. General anesthesia was induced whereupon he died suddenly.

Autopsy Findings. At autopsy the lungs were heavy and rather soggy with widespread congestion and moderate edema but there were no emboli or infarcts in either lung. The heart was somewhat enlarged as a result of dilatation of the left ventricle and the pericardium was universally agglutinated by a rather tough fibrinous exudate binding together the parietal and visceral layers. The source of the pericarditis was revealed as a wide area of recent myocardial necrosis in the posterior wall of the left ventricle, involving the entire thickness of

the wall except for an outer layer of thinly stretched muscle and epicardium through which some hemorrhage had seeped into the pericardial sac. The area of necrosis had a yellowish-white caseous appearance and was surrounded by a rather broad zone of hemorrhage side by side with areas of grayish cooked-meat appearance and hemorrhagic mottling extending into the right ventricle and interventricular septum. A large area of mushy friable soft reddish-black mural thrombus filled a large portion of the left ventricle in its posterior recesses overlying a large area of white thrombus adherent to the area of infarction. The right coronary artery was completely occluded by recent white and red thrombus throughout most of its horizontal course. Moderately severe atherosclerosis with calcification and narrowing was present also in the major branches of both coronary arteries. Anemic infarcts resulting from embolism were found in the spleen and right kidney without significant hemorrhage. No areas of ulceration or hemorrhage were found in the gastrointestinal tract and the mesenteric vessels were patent. There was no peritoneal hemorrhage, exudate, or ascites.

The most striking finding in the case was the presence of massive bilateral hemorrhage in the adrenal glands, which were swollen symmetrically to a striking degree, weighing together 60 grams. The substance of each adrenal was replaced by what appeared to be ordinary blood clot and the residual cortex as seen microscopically was reduced to a thin remnant of necrobiotic tissue with an exceedingly narrow layer of viable cells in the extreme outer margin.

DISCUSSION

Anticoagulant therapy as currently employed in the treatment of myocardial infarction is rarely complicated by hemorrhage in tissues which have previously been normal. Even the infarcted portions of the heart muscle are rarely so affected in significant degree. In the case under discussion it transpired ultimately that the dosage of heparin had been manifestly insufficient to prevent formation of a large mural thrombus within the infarcted ventricle or to protect against peripheral embolism. Throughout the period of administration of heparin the clotting time rarely extended beyond 14 minutes. At autopsy a limited degree of hemorrhage was disclosed in the margins of the ventricular infarct. The only other evidence of hemorrhage was that revealed in the adrenal glands. It is unlikely therefore that the use of heparin was the sole responsible factor in the localization of massive symmetrical hemorrhage in the adrenal glands. Theoretically the severe pain and circulatory weakness which accompanied the myocardial infarction and the protracted use of vasopressor amines, by provoking increased adrenocorticotrophic activity of the anterior pituitary, may have been important contributory factors to adrenal hemorrhage in addition to heparin. However even this sequence, judged by the experience gained by many observers in large series of cases of coronary disease treated with anticoagulants, appears insufficient in itself to have caused massive adrenal hemorrhage. The suspicion is therefore inescapable that administration of corticotropin, given during a 6 day period while this severely stressed patient was also receiving heparin, played the decisive role in the final eventful outcome.

SUMMARY

The case of a patient suffering from myocardial infarction is described in whom corticotropin had been given in an effort to overcome bloody diarrhea which complicated heparin therapy. Signs of a retroperitoneal complication developed culminating in fatal collapse. Autopsy revealed bilateral symmetrical hemorrhagic necrosis of the adrenal glands. This unusual complication of myocardial infarction centers attention on the risk in corticotropin therapy of provoking changes in the adrenal cortex which predispose to hemorrhage when heparin is administered simultaneously.

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INFLUENCES OF ADRENAL HORMONES ON AORTIC HISTOPATHOLOGY IN RELATION TO BLOOD LIPOPROTEINS IN RABBITS

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In a recent summarizing discussion on atherosclerosis, the late Professor Duff restated the two principle factors probably most concerned in the pathogenesis of this disease: (a) a disturbed lipid metabolism, and (b) local factors in the arterial wall that operate to permit and promote the deposition of lipids in particular areas (1). While the problem of abnormal plasma lipid distribution in association with experimental atherosclerosis has been abundantly presented in the literature (2, 3) practically no attention has been given to observing aortic morphology concurrently in these studies. Certain reports in the recent literature (4-10) suggest that hormonal-treated rabbits might provide an experimental approach to investigations of the interrelationships of systemic and local factors, if indeed this exists. Cortisone administration was shown to inhibit, retard, or even induce regression of atherosclerosis in cholesterol-fed rabbits (4, 6, 7, 9, 10). On the other hand, degenerative changes in aortic media were demonstrated after relatively short periods of epinephrine administration to rabbits provided the regular laboratory diet (8, 11). Further, these hormonal treatments significantly affected some aspects of lipid metabolism in plasma and aorta.

In the course of studies of the influence of hormones upon lipid distribution and metabolism in normal- and cholesterol-fed rabbits we took comparable sections of the aortic arch for histological examination. The present report is concerned with the histological findings in aortae in relation to certain features of plasma lipid constitution determined concurrently in rabbits administered epinephrine or cortisone.

MATERIALS AND METHODS

Mature, female rabbits of pure-bred stock were used. Rabbits on high-cholesterol diet were given 1 gm. of crystalline cholesterol (Merck, U.S.P.) mixed thoroughly with 15 gm. of shredded carrots, in the morning and afternoon, and 125 gm. of rabbit pellets daily. Control rabbits received the carrot portion without additive. These supplemental rations were readily and entirely consumed each day. Cortisone acetate (in physiological saline) was injected intramuscularly in doses of 10 mg. per rabbit. Epinephrine (Adrenalin, aq., 1:1000) was administered intravenously as a single injection in doses of 0.025 mg. kgm. of body weight for each of five days and 0.05 mg. kgm. on each of nine following days.

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Controls received equivalent amounts of physiological saline. Specific details of hormonal treatment and duration of cholesterol-supplemented diet are presented in the RESULTS section. Plasma cholesterol was determined by the method of Schoenheimer and Sperry (12). Determinations of Standard S_f 0-12 and S_f 12-400 classes of serum lipoproteins were done by arrangement at the Institute of Medical Physics, Belmont, California.

The whole aorta was removed from rabbits immediately following an intravenous overdose of EVIPAL. The vessel was cleaned of adherent tissue; graded for atherosclerosis by visual judgment and a section of aortic arch then was fixed in formalin for later histological examination. The remainder of this tissue was used in chemical and radioactivity analyses the results of which are reported elsewhere (9, 10, 13). The fixed specimens of aortic arch were embedded in paraffin, and sections cut and stained with hematoxylin-eosin, Weigert's Elastic-Van Gieson, and Alcian Blue-PAS (14). The Van Kossa stain for demonstration of calcium was applied in some instances.

RESULTS

Aortic Morphology of Normal Rabbits Treated with Epinephrine and Cortisone. The microscopic examinations of aortae of rabbits given single, daily, intravenous injections of epinephrine alone for 14 days presented medial degenerative changes typical of that first reported by Josue (11). It is noteworthy that occasionally a small area of similar medial alteration was seen in a few of the untreated rabbits. A representative section of aorta from an epinephrine-treated rabbit is presented in Figure 1 A. The medial changes consisted principally of coarse thickening of elastic fibers in small and confluent areas, necrosis and destruction of segments of elastic fibers, and some of the necrotic areas stained strongly positive with the PAS method. Areas of diffuse calcification as well as calcification of individual elastic fibers also were seen. These changes were associated with proliferation of fibroblasts, a few lymphocytes, and occasionally multinucleated giant cells were observed. In some sections the interfibrillary ground substance appeared swollen and stained positively with Alcian-Blue suggesting the presence of acid muco-polysaccharides. The intima appeared unaffected in all observed cases.

In Figure 1 B is presented a section of aorta from a rabbit treated with epinephrine and cortisone concurrently for 14 days. Although examination showed medial degenerative changes similar to that seen in rabbits treated with epinephrine only, there appeared definitely to be less fibroblastic proliferation and cellular reaction. This observation is in accord with reports that cortisone acts upon all components of ground substance and exerts a markedly retarding influence upon proliferation of fibroblasts (15).

Determinations of plasma lipids distribution in epinephrine-cortisone treated rabbits showed that phospholipid, total cholesterol and neutral fat concentrations were 3, 3 and 9 times greater than the respective levels of control rabbits (130 mg%, 66 mg% and 162 mg%) while concentrations of aortic lipid fractions were not different from controls (16). In contrast, a two-fold rise in

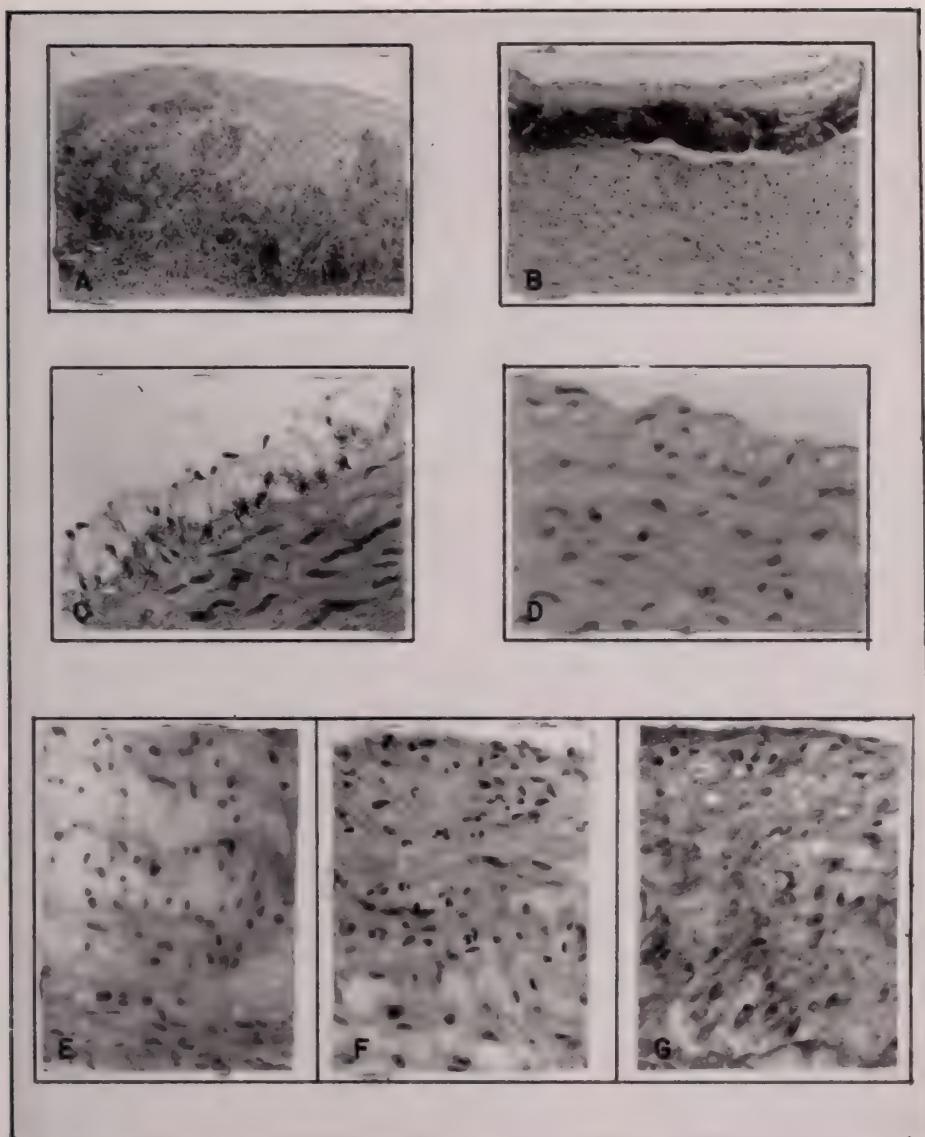


FIG. 1. Representative hematoxylin-eosin sections of aortae from rabbits administered epinephrine and cortisone, on regular laboratory diet and high-cholesterol diet.

A. From rabbit fed regular laboratory diet and administered epinephrine intravenously, daily for 5 days at dose of 0.25 mg/kgm and then for 9 days at dose of 0.05 mg/kgm. B. From rabbit similarly treated with epinephrine as above, and simultaneously receiving 10 mg of cortisone intramuscularly. C. From rabbit on cholesterol-supplemented diet for 35 days and injected with physiological saline (0.4 cc) intramuscularly. D. From rabbit on same dietary regime as above and also daily injected intramuscularly with 10 mg of cortisone. E. From rabbit consuming a high-cholesterol diet for 100 days. F. From rabbit on same dietary regime and also receiving 10 mg of cortisone intramuscularly, 3 times per week for the entire period of the diet. G. From rabbit on high cholesterol diet for 120 days and administered 10 mg of cortisone intramuscularly, daily on the last 14 days of the dietary regime.

plasma neutral fat level was the only change in rabbits that received epinephrine alone.

Influence of Cortisone on Aortic Morphology of Cholesterol-Fed Rabbits. Retardation of development and regression of gross atheromatous lesions in aorta of rabbits on a high cholesterol diet and concurrently treated with cortisone has been reported (4, 7, 10). The mode of action of cortisone in this phenomenon is unknown. Furthermore, the nature of the specific histological alterations in the aorta of these animals, which is believed to be particularly germane to the problem of pathogenesis of atherosclerosis, has heretofore not been described. We have examined sections of aorta of rabbits fed a high cholesterol diet for 35, 70, 100 and 120 days and compared the morphologic picture with observations made on aorta of rabbits fed this diet and treated with cortisone. The degree of aortic intimal change in cholesterol-fed rabbits is related to the duration of the dietary period. After 35 days a very mild change—a single layer of typical “foam cells”—was observed in the intima. Aortic morphology was much more affected in rabbits on the cholesterol diet for longer periods. The changes appeared as scattered plaques or in a rather diffuse distribution forming multiple layers of “foam cells.” Occasionally, small groups of these cells were seen in the most superficial layers of the media and in some instances splitting of elastic fibers was observed.

In Figure 1 C is presented a representative section of aorta from a rabbit on high cholesterol diet for 35 days, and in Figure 1 D is shown a section of aortic arch of a rabbit on this dietary regime and administered a single, intramuscular injection of 10 mg. of cortisone acetate each day the entire period. It may be seen that intimal changes were absent in the aorta of the animal treated with cortisone. Since, aside from the factor of time, hypercholesterolemia is generally believed to be an important factor in development of atheromata, a comparison of plasma cholesterol levels in these animals is of interest. In cortisone-treated rabbits the average plasma total cholesterol was 1550 mg./100 cc. of plasma while that of the untreated cholesterol-fed rabbits was 1440 mg./100 cc. of plasma. These values were approximately 15 times greater than that of controls (rabbits fed the regular laboratory pellet-food diet).

In Figure 1 E is shown a representative section of aorta from a rabbit on high cholesterol diet for 100 days. The lesion is typical of aortic intimal changes found in rabbits consuming this type of diet for three to four months. In contrast is the morphologic picture of an aorta from a rabbit given a high-cholesterol diet for 100 days and also injected three times each week with 10 mg. of cortisone (Fig. 1 F). Only scattered, small, intimal plaques were observed in only a few animals treated in this manner. The plaques, where present, contained only a small number of “foam cells” while major portions of the plaques were composed of fibroblasts, delicate connective tissue fibers and a few lymphocytes and neutrophilic leukocytes. Also noted were small scattered areas in the interfibrillary ground substance of the media that appeared slightly swollen and stained positively with Alcian Blue. The marked differences between the untreated and cortisone-treated, cholesterol-fed rabbits with regard to overt atherosclerosis and structural organization of the atheromatous plaques were

even more remarkable in view of their plasma cholesterol levels. In the specific cases represented by Figures 1 E and 1 F, plasma total cholesterol concentration was 736 mg. 100 cc. of plasma while the total cholesterol level of the rabbit treated with cortisone was 2000 mg. 100 cc. of plasma. Thus, the lesions in the cortisone-treated animal were only minimally developed although its blood cholesterol level was three times greater than the rabbit fed high-cholesterol diet and untreated.

The relationship of cortisone to atherogenic processes is indicated especially by evidence that administration of this substance not only retarded plaque development but also promoted regression of atheromatous lesions in cholesterol-fed rabbits. Figure 1 G shows a section of aorta from a rabbit (representative of the entire group) fed a high-cholesterol diet for 120 days and had received single, daily, intramuscular injections of 10 mg. of cortisone on each of the last 14 days of the dietary regime. Visual inspection indicated that overt aortic atherosclerosis in these rabbits was at least half as severe as that seen in the untreated, cholesterol-fed rabbits. Microscopic examination presented a rather high percentage of fairly large intimal plaques in the aortae. However, the number of typical "foam cells" was rather small in relation to the size of the plaque. Instead there were numerous, fairly large, confluent, vesicular spaces which stained positively with Alcian Blue. A moderate number of fibroblasts, lymphocytes, and delicate connective tissue fibers were also seen. These findings were in contrast with aortae of rabbits given the high-cholesterol diet only for the same period where the "foam cells"—indicative of lipoid infiltration—constituted the principle element of the intimal plaques. In these animals, too, hypercholesterolemia appeared unrelated to the apparent severity of aortic intimal involvement. The average plasma cholesterol level in untreated, 120 days cholesterol-fed rabbits was 1113 mg. 100 cc. of plasma while this lipid in the cortisone-treated group averaged 1248 mg./100 cc. of plasma.

Recent evidence is suggestive of a relationship between circulating-blood lipoprotein levels and atherosclerosis (17, 18). In Figures 2 A and 2 B are presented the summarized data of Standard S_f 0-12 and S_f 12-400 classes of lipoproteins determined in some of the rabbits whose aortic morphology was described. The concentration of S_f 0-12 lipoproteins was three times greater in rabbits on a high-cholesterol diet for 70 days compared with controls fed a regular laboratory diet while the S_f 12-400 class experienced very little change. Cortisone administered thrice weekly (10 mg. each injection) to normal-fed rabbits for a 70-day period resulted in significantly decreased concentration of the S_f 0-12 lipoproteins and the level of S_f 12-400 class was markedly increased compared with controls. On the other hand, in cholesterol-fed rabbits similarly treated the S_f 0-12 and S_f 12-400 classes of lipoproteins were increased 100% and 200%, respectively compared with untreated, cholesterol-fed rabbits. In Figure 2 B are summarized the changes in lipoprotein levels of rabbits on normal- and high-cholesterol diets for 120 days without treatment and after a final period of daily, single injections of 10 mg. of cortisone for 14 days. It is shown that cortisone treatment of these animals resulted in marked elevation of the

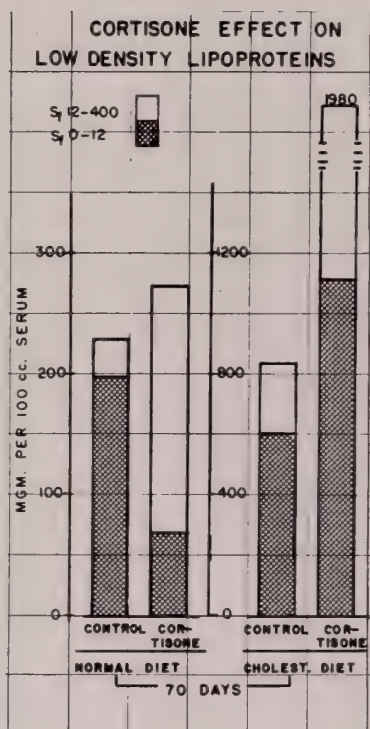


FIG. 2 A

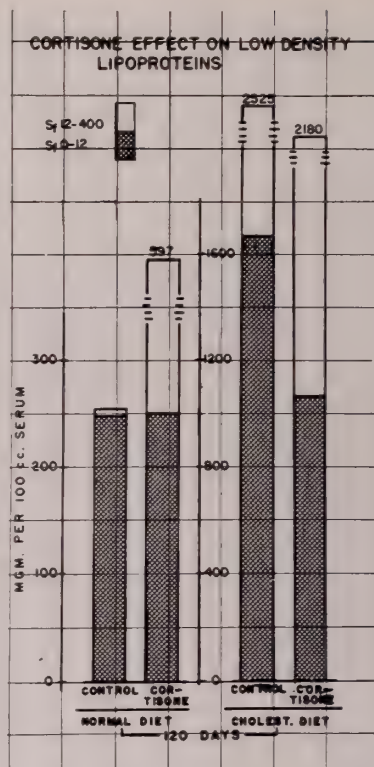


FIG. 2 B

FIG. 2. The influence of cortisone on concentrations of Standard S_f 0-12 and S_f 12-400 classes of serum lipoproteins of rabbits on regular laboratory diet and high-cholesterol diet for different periods. See text for dose of cortisone and injection procedures used. (Analyses of blood samples were done at Institute of Medical Physics, Belmont, Calif., by arrangement.)

S_f 12-400 class of lipoprotein concentrations. The significant feature of cortisone administration on the levels of the lipoprotein classes demonstrated by those data was the marked elevation of the S_f 12-400 class relative to the change in S_f 0-12 lipoprotein concentrations.

COMMENT

Studies on the pathogenesis of atherosclerosis are presently based on the operative concept that the disease is associated with a disturbance in lipid metabolism and possibly related to regional factors in blood vessel walls. Since hormones are probably the most important endogenous factors regulating lipid metabolism, their role in atherogenic processes needs elucidation. The focal, necrotic areas observed in aortae of epinephrine-treated rabbits of this study are in accord with that reported by Josue (11). However, the cellular reaction was markedly less when cortisone and epinephrine were administered simultaneously. It is interesting that these two hormones which are known to interact in metabolic processes, also manifest themselves visibly as morphologic alterations of arterial tissue. The

nature of their relationship and effects upon local, structural alterations in aortic tissue cannot be explained with the evidence presently available.

The observations of special interest are the focal alterations in structural elements of aortic intimal tissue in cortisone-treated, cholesterol-fed rabbits. Until recently it was generally held that a high blood cholesterol level, prevailing over a period of time, was critical for the development of atheromatous lesions. However, more recent studies in alloxan-injected (4, 5), and cortisone-injected (7, 9, 10), cholesterol-fed rabbits have raised the question whether high blood cholesterol levels, per se, may be the primary factor in development of atherosclerosis. In this study, histological evidence of inhibition of development of atheromatous lesions and even regression of such lesions was presented in cortisone-treated rabbits. Moreover, this effect on aortic morphology was found although the blood cholesterol levels were as high or greater than that of untreated rabbits. On the other hand, the cortisone-treated rabbits experienced marked changes in the components of their lipid-transport mechanism, namely, significantly increased concentration of the S_f 12-400 class of lipoproteins in association with a large rise in plasma neutral fat level (9, 10). Albrink et al. (19) recently reported evidence that under such conditions lipid can dissolve cholesterol existing in plasma. The question which still must be resolved is whether cortisone's apparent effect on the morphologic aspects of atherosclerosis is the resultant of processes directly related to the morphological integrity of arterial tissue or rather its action upon lipid-transport mechanisms preventing cholesterol deposition.

SUMMARY

The histopathologic alterations in the aortic media of epinephrine-treated rabbits and the intimal changes of cholesterol-fed rabbits for 35, 100 and 120 days were markedly modified when the animals were also treated with cortisone. In cholesterol-fed rabbits intimal structural organization suggested collapse of "foam-cells" and reformation of the interfibrillary ground-substance and connective tissue network. These morphologic changes were discussed in relation to the blood cholesterol levels in these cortisone-treated rabbits and the marked changes in Standard S_f 0-12 and S_f 12-400 circulating-blood lipoprotein levels experienced in these animals compared with untreated, cholesterol-fed rabbits.

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UNITY IN PATHOGENESIS AND GROSS PATHOLOGY OF THE PYOGENIC AND TUBERCULOUS BRONCHOPNEUMONIAS

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The clinical studies of Glass and Kramer carried out in Dr. Klemperer's laboratory at The Mount Sinai Hospital established the clinical significance of the bronchopulmonary segment. That a pulmonary lobe consisted of the juxtaposition of bronchopulmonary segments had long been known by the anatomist, the embryologist, and the pathologist, but the application of this knowledge to the problem of airborne infection within the bronchopulmonary unit was first set forth by Glass. His work was of fundamental importance in the study of bronchogenic infections of the lungs, carried out for many years by the then constituted Thoracic Group of The Mount Sinai Hospital (H. Hennell, R. Kramer, H. Neuhoof, C. B. Rabin, A. S. Touroff and H. Wessler). On the basis of examination at autopsy and of tissues removed at operation as well as of lesions noted at operation, certain conclusions were reached concerning the suppurative bronchopneumonias and pulmonary abscess, which will be briefly set forth.

The concept of anaerobic infection leading to putrid pulmonary abscess postulates the arrest of infected particulate material in a bronchus of a bronchopulmonary segment. A severe necrotizing bronchitis at the site of arrest ensues, soon followed by a rapidly descending infection into the parenchyma of the segment. Intense pleuritis over the involved segment is a constant and early feature (initial severe thoracic pain). Dense adhesions which agglutinate the visceral and parietal pleura are the result. Necrosis of the bronchial wall and parenchyma which is extensive, has been termed "necrosuppurative" as descriptive of this type of bronchopneumonia. Expectoration of foul pus by way of perforation of the bronchus permits the entry of air into the abscess (air in the abscess cavity is not referable to anaerobic bacteria). The size of the cavity is not necessarily commensurate with the extent of destruction of the pulmonary parenchyma, for the distracting force of coughing (combined with a form of valve-like action at the site of perforation) tends to balloon the cavity. Autopsy examination of fatal cases of putrid pulmonary abscess demonstrated a high incidence of necrosuppurative pneumonia in other bronchopulmonary segments, both adjacent and remote. The original lesion was repeated in varying degrees, including abscess formation. The infection of other segments was evidently due to aspiration into them of pus from the original lesion. The term "spillover" was attached to this bronchial spread of the infection. The involvement of adjacent segments was apparent at operations performed for large pulmonary abscesses, as well as at autopsy.

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Concerning the pathogenesis of *aerobic* suppurative bronchopneumonia, infection descends from a main bronchus into more than a single bronchopulmonary segment in most instances. The area of involvement rarely presents the degree of necrosis and destruction of bronchial wall seen in putrid pulmonary abscess (in adults, less rare in infants and children). Overlying pleuritis may be insignificant (initial pain usually mild), and adhesions limited. Spillover to other lobes was common in the pre-antibiotic era. When massive necrosis is severe enough to warrant the term "necrosuppurative" bronchopneumonia, an abscess-like lesion evolves. Following expectoration of its contents a cavity may appear, whose x-ray appearance closely resembles that seen in tuberculosis. The appearance may be so similar that it is of interest to trace the manner of evolution in serial roentgen films of a typical case. An initial film portrays the homogeneous shadow characteristic of bronchopneumonia, in which, however, highlights may be discerned representing areas of rarefaction. Following profuse expectoration, a film now reveals a substantial thick-walled cavity with fluid level, and a later film, a large, virtually empty cavity enveloped by a shell of compressed lung. Because of the parallel features of a tuberculous lesion, the appearance of a case like the foregoing at operation (occasionally performed in the pre-antibiotic era) will be briefly described: Agglutinating visceroparietal adhesions are limited and not dense. A thin shell of compressed lung (already undergoing organization and fibrosis in two to three weeks from the onset of illness) is traversed to enter the cavity. The appearance of the cavity suggests an older lesion, being smoothly lined for the most part and presenting the rounded orifices of one or more bronchi.

The evolution and morbid anatomy of tuberculous bronchopneumonia will be outlined in accordance with the foregoing, without regard to other factors of importance such as extension by way of the lymphatics and blood stream. Initiated at the site of arrest of material bearing tubercle bacilli (droplet infection), which is aspirated into the bronchus of a bronchopulmonary segment, a tuberculous bronchitis is set up. Downward extension into the parenchyma ensues. Pleuritis over the involved segment usually is not severe (pain usually insignificant) and agglutinating visceroparietal adhesions accordingly are not usually dense. Ulceration of the bronchus and caseation necrosis of the parenchyma set the stage for evacuation of the contents and the formation of a cavity. A ballooned cavity under tension enveloped by a thin shell of abscessed parenchyma represents, in fact, a smaller area of destruction of the lung than appears to be the case in the roentgen film (as in the pyogenic lung abscesses). Spill-over infection into adjacent as well as remote bronchopulmonary segments was common before the antibiotic era.

The parallel features in pathogenesis, morbid anatomy, and gross pathology of the aerobic, anaerobic and tuberculous bronchopneumonias suggest a unity for all airborne infections within the bronchopulmonary segment. The concept is of some theoretical interest, and an understanding of the parallelism which exists is of medical as well as of surgical significance.



Hungarian Post Travelling.

MATERIALS FOR A PORTRAIT OF RICHARD BRIGHT AS A YOUNG MAN

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A book of travels can be read not so much for its descriptions of places seen and events experienced as for the portrait it draws of the mind of the traveller; a book rich in such revelation is "Travels from Vienna through Lower Hungary; with some Remarks on the State of Vienna during the Congress in the Year 1814", by Richard Bright, recently graduated in Medicine from the University of Edinburgh.

To attempt a critical analysis of this weighty quarto of some 600 pages would be indeed a work of supererogatory presumption, as the greatest of American medical historians, Fielding Garrison, has shown both by excerpts from its text and his scholarly comments on them why it may be considered the best book of travels ever written by a physician (1). The present writing is therefore no essay in historical or literary criticism, but seeks only to let young Bright reveal in his own words, with as little comment for orientation as is needful, his reactions to novel sights and new experiences. Thus the reader can "see" young Richard "plain", for it is his youth that must be kept in mind, and in the self-drawn portrait of the physician as a young man he will recognize the master of medicine that was to be.

In the summer of 1814, the way being at last opened by the apparently secure confinement of Napoleon in Elba, Bright departed for his travels on the Continent. It began in the conventional manner of a *Wanderjahr*, with the first weeks spent in Holland and Belgium followed by professional studies of a few months at the *Charité* in Berlin. But these were no times for pedestrian peregrinations and the journey assumes more the aspect of a *Grand Tour* as the lure of that "most extraordinary assemblage" in Vienna drew the young man of 25

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from the austerities of academic activities to the city, where, as he quotes the then current saying, "*Le Congr s danse, mais il n'avance pas.*"

First prospects of a foreign city are often depressing;

I soon procured a lodging in a busy and dirty inn in the commercial part of the city—my apartment was large and desolate, without a carpet . . . the windows, however, which were double looked into a busy street lying in the direct line between the gayer parts of the town . . . and as it was an hour when many carriages were rolling towards that spot (the Prater) the scene was lively, and put me more in mind of London than any thing I had before seen in Germany.

The next day, though Sunday, brought even greater liveliness as young Bright finds his bearings.

I was strongly recommended to visit a place of public amusement called the Redoute, where, in all probability, I should see many of the distinguished persons then collected at the Congress.

Not having yet delivered my letters, I accompanied a gentleman of Vienna, with whom I had made an accidental acquaintance. We entered the room about nine o'clock in the evening. It is a magnificent saloon, finely lighted, surrounded by a gallery, and forming a part of the large pile of building called the Bourg or Imperial Palace. Never was an assembly less ceremonious; every one wore his hat; many, till the room became heated, their great-coats; and no one pretended to appear in an evening dress, except a few Englishmen, who, from the habits of our country, and some little vanity, generally attempt to distinguish themselves by an attention to outward appearanc . Around the whole circumference of the room were four or five rows of benches, occupied, for the most part, by well-dressed females; while the other parts presented a moving multitude, many of whom were in masks, or in dominos, and were busily engaged in talking and laughing, or dancing to the music of a powerful orchestra. My companion squeezed my arm, as we passed a thin figure with fallow shrunken features, of mild expression, with a neck, stiff, bending a little forwards and walking badly. "That is our Emperor." I shook my head and smiled. He was alone, and dressed like the rest. "Pray allow me to doubt a little till I have some farther proof."—"There, do you see that little man with white hair, a pale face, and aquiline nose? He was almost pushed down as he passed the corner;—that is the King of Denmark." Again I shook my head in disbelief. "Here the Emperor of Russia approaches." I looked up, and found the information true. His fine manly form, his round and smiling countenance, and his neat morning dress, were not to be mistaken; they were the same which, some months before, I had seen enter the church at Harlem, to the thundering peals of the grand organ. I soon recognised the tall form, the solemn and grave features, of the King of Prussia; and afterwards seeing these two in familiar conversation with the two monarchs, whose pretensions I had disputed, was satisfied their claims were just. . . . "Here, turn your eyes to that seat. The large elderly man, with a full face,—he looks like an Englishman,—he is the King of Bavaria."—"Pardon," I exclaimed, stepping quickly aside. "That was the Grand Duke of Baaden," said my monitor, "whose toe you trod upon". . . .

As the night advanced, refreshments were provided for those who paid for them, in apartments fitted for the purpose, and several rooms were opened, adjoining to the gallery, where the company might order suppers; and the whole did not break up till a late hour in the morning. Such was my first introduction to some of the members of the Congress.

There follows some 50 pages of descriptions of horse shows at the Imperial Riding School, suppers, Grand Court on New Year's Day, a "species of Royal Hunt," staged in an arena with the audience of royal participants shooting from their boxes, an exhibition he thought "deprived of the noblest features of this

manly amusement, and degenerated into a cruel display of skill in a very ordinary art," assemblies, "Pic-nic balls"; all are observed and described with the objective and critical comments of one who participates with a controlled enthusiasm that never loses its sense of values. There is always a measured balance, for every pro, a con; of the uniforms of the Imperial officers "so interwoven with gold, clasped with jewels, such diamond plumes, and such embossed stars and orders" but "they bore the appearance of being the substantial fruits rather than the honorable testimonials of victorious arms." The 300 Imperial carriages "painted green and adorned with either silver or gold", . . . "many of them approached, though none of them equalled, either in elegance or workmanship, the best English carriages".

The validity of any such critical reportage obviously depends on the nature of the evidence gathered; Bright early showed that in all things he thought it best to go to sources for first-hand information, even if the access might seem unapproachable. Word had reached Vienna that Napoleon was on the loose again; but let our young man describe his reaction:

Whatever might be the political feeling with which the fallen Emperor was viewed, (how many Englishmen would have written Bonaparte, if not Buonaparte or even the Corsican Bandit), it was unmixed commiseration alone which could attend the misfortunes of the Empress and her guiltless child. I was one day tempted by curiosity; if the interest of the object may not deserve a better name; to transgress so far the limits of propriety, as to call with a friend at the palace of Schönbrunn, and request that we might be indulged with an introduction to the infant king. We found that all the servants about the palace were Frenchmen, who still wore the liveries of Napoleon. When our request had been made known, a female attendant came to the antichamber and told us, that the child was at present with its mother; but if we could amuse ourselves for an hour in the gardens, and would then return, our curiosity should be gratified. We accordingly came at the appointed time, and were ushered into a room where the infant was sitting on the floor amusing himself, amidst a profuse collection of playthings. We were introduced to Madame Montesquieu, and one or two other ladies who were present. The infant king of Rome; then indeed styled the Prince of Parma; was at the moment occupied with a toy, which imitated a well-furnished kitchen. He was the sweetest child I ever beheld. His complexion was light, with fine white silky hair falling in curls upon his neck. He was dressed in the embroidered uniform of an hussar, and seemed to pay little attention to us as we entered, continuing to arrange the dishes in his little kitchen. I believe he was the least embarrassed of the party. He was rather too old to allow of loud praises of his beauty, and rather too young to enter into conversation. His appearance was so engaging that I longed to take him in my arms, yet his situation forbade such a familiarity. Under these circumstances, we contrived a few trifling questions, to which he gave such arch and bashful answers as we have all often received from children of his age, and, after a few minutes conversation with Madame Montesquieu, we withdrew.

There then follows a description of a later conversation with friends on the difficulty of obtaining good historical evidence:

"Nay," said a lady in the company, "I think it might easily be done, if people were a little more in the habit of noting down events which are taking place around them." "Even then," replied a gentleman, "it is much more difficult than you imagine. Take, for instance, the fact which is said to have occurred amongst us within these few days, I mean the attempt to carry away the infant King of Rome."

Bright makes no comment to the company on his recent visit to Royalty, but turns the conversation to the general subject of stratagems and conspiracies and concludes:

In one fact alone were we all pretty well agreed,—that the infant King had been very suddenly transferred from Schönbrunn to the more secure apartments in the Royal Palace of Vienna, where, for the last two days, he had been exhibited pretty constantly from a window looking into the great square.

On the political problems of the Conference and the prolonged attempts at their resolution, Bright is brief; the reason for this reticence is clearly not a lack of interest, but is perhaps apparent in a somewhat cynical comment on what he calls the "difficulties" of diplomatic procedure; one has only to change the names of the distressed countries, the champions of the right, and the villains to make a modern reading pertinent to the present day:

The grand subjects in discussion were the future condition of Poland, Saxony, and the Italian States,—in fact, all those points in which political expediency appeared to be in opposition to justice. It was the difficulties arising on these subjects which caused the proceedings of the Congress to be so long and tedious,—so many different interests to be consulted, so many scruples to be overcome, and so many just and honest men to be perverted from their ways;—what wonder that some months should have elapsed in consulting, in protesting, and in recanting. Of what notes and memorials,—of what representation and concessions—did we not daily hear: of sturdy ministers who faltered, and of faltering ministers who grew firm. In the midst of all these rumours, it was ever the anxious inquiry, whether England was the steady champion of justice?—whether she boldly asserted and strenuously maintained that character which she boasted freedom of her principles led Europe to expect, and which her preeminence, both in arms and finance, seemed to have placed her in a condition to retain? I would, however, caution those skilful diplomatists, who, sitting at their ease, like the champions at a carrousal, know how to vanquish Turk and Moor without sustaining a blemish, not rashly to decide on events, the complicated causes of which must be sought in every remote corner of Europe; in the interests, the perverseness, the weakness, or the wickedness, as well as the right feelings of every potentate and minister in the civilized world. . . . I will not, however venture farther upon these disputed points; but will rather conclude a chapter, the object of which has often been to present the scenes of life, enriched by wealth, and ennobled by royalty, by conducting my reader to a gloomy cave, where he may associate with more emperors and empresses now brought low, and more of royal birth, than ever graced the assemblies of a Congress. In an extensive vault beneath the chapel of the Capuchins, in the Mehl Grub, we visited the cemetery of the imperial family.

The somewhat turgid romanticism of this conclusion, which either is a reflection of the then current neo-gothic lucubrations of Mrs. Radcliff or perhaps is to be considered only as an example of the premature premonitions of mortality that youth at times finds appropriate to serious discourse, should not deceive us into believing that young Bright is not enjoying himself immensely, albeit with a certain controlled restraint which is more common to greater maturity. Gaiety never quite gets out of hand, nor do its frivolities escape the critical eye:

Morning calls, those senseless conventions of society, are not considered of the same importance in Vienna as in London.—The (domestic) evening amusements in Germany are very various, and will sometimes almost fall under the dreaded denomination of puerile—not content with requesting young ladies to recite verses, they will sometimes invert the

natural order of things and compel children to act plays, while grown people will play cross questions and crooked answers. Acting riddles is a favorite game and one well calculated to amuze (and here surely speaks the voice of wisdom to the unfortunate laggard at the modern cocktail party) those, who wisely resolve to be amuzed when they can.

And if these homely pleasures pall, there is ready access to more lively diversions:

After seeing this exhibition, I went to a little card party, and afterwards to one of the masked balls at the Redoute, where I laughed with great princes, and flirted with masked ladies, till a late hour, and thus concluded a Sabbath (apparently indeed Continental!) in the capital and court of this most Christian and Catholic country.

But little card parties, dancing and flirtation were not the purpose of this young man's journeyings and in March of 1815 Bright left Vienna (title piece) for the serious business of a survey of the then present state of Hungary. For some 600 pages he reports on every aspect of its geography, its culture, its people and its religious, economic and political organization that were accessible to a persistent investigator. Nothing escapes his attention in description and nothing eludes his analysis on retrospection.

As the economy of Hungary was based largely on its horticultural and its mineral wealth, it is the princely estates and mines and the detail of their management that comprise the bulk of Bright's report. There is no reason to believe that his interest had previously been particularly engaged in rural activities; he was the third son of a wealthy merchant-banker in Bristol and though a distant relative and the current head of the family held a manor and estate in Herefordshire, Bright's life had been spent in acquiring a classical education in the cities of Bristol, Exeter and Edinburgh. Yet he felt, as he states in his foreword that

It is the humble duty of the Traveller to collect, under all the varieties of circumstance, such materials as may supply a ground work for connected history, and for general deduction. Correct observation and faithful statement are the cardinal virtues on which his character must depend . . . (a statement of principle that was to be exemplified with such distinction in his later medical achievements.)

We cannot give here even one complete example of his meticulous collection and analysis of, say, the agronomic data of a typical princely estate; for pages he outlines and comments on crop rotation, the return of individual parcels of meadow land, the breeding of horses, cattle and sheep, in the latter case with elaborate detail as to the records kept of pastorage and schedules of shearing, all this not only in the text but in great folding tables which proceed to such minutiae as standard equivalents of different fodders and which list in one column 42 varieties of plants, beginning with "Sweet Hay, one pound," and ending with "Quisquiliis, one and half pounds".

Again we see that all this labor is not so much the selection of his personal interest as a part of the job which confronts him, for when a religious establishment is visited the contact leads to tables of organization of the Hungarian clergy, Catholic, Lutheran and Jewish from the Archduke-Archbishop, Primate of all Hungary, down through the 207 Prebendaries to the 1928 Assistants to Local Chaplains. Mining, with tables of ore production, methods of smelting and techniques of assay accompany his progress through the mountainous areas, all

elaborated with comparisons of their efficiency to similar procedures in other countries. An outline of educational policies in Hungary accompanies his description of Buda-Pesth. The University is described and the organization of its Faculty with a brief resume of its medical school. It is typical of Bright that here again he is not influenced by personal predilections; it receives competent but not excessive treatment. One comment will interest the present-day medical educator who at times may feel overwhelmed with the magnitude and diversity of his administrative problems. Speaking of the University teaching hospital:

I was much pleased with the order and regularity with which this hospital was conducted; and am not sure that more celebrated institutions might not gather hints from the proceedings of this distant and almost unknown medical school.

And here, perhaps, Bright anticipates the source of many of our present-day difficulties:

It must, however, be owned, that the whole is more manageable from its small extent as there were not . . . above 30 in the earlier years of their medical studies.

It speaks well for the Hungary of that time and of the young man's latitudinarian attitude when he concludes:

And to convey some idea of the liberality which exists in this establishment, disdaining to embarrass the progress of science by combining with it the dogmas and religions, and exacting, as the price of its comparatively trifling attainments, the sacrifice of truth, and the outward confession of some creed to which the heart does not consent, it will be enough to state, that, amongst the students in this Catholic country, many professed the evangelical Lutheran doctrines, many were of the Reformed church, many of the Greek church who had refused to conform, and many who were Jews. It is a lesson which leaves no room for comment; . . . that in the education of this small fraternity of Jews, of Greeks, of Protestants and of Catholics, no fewer than 92 Professors and Assistants find their daily occupation.

And so young Bright proceeds; everything that meets his eye is grist to the mill of an inquiring and analytical mind. It might seem that this mass of factual data would swamp the reader with its sheer bulk, but through the cloud of reportorial and statistical data there breaks through from time to time the genial humanity of a liberal spirit.

Love of natural beauty for example; and this he expresses not only in his descriptive prose but in visible form in the sketches he made during his progress and which are reproduced in engravings, the mellow tones of which delight the eye. One of these is illustrated in our modern crude half-tone (Fig. 1). Bright had an eye for quality of line and tone in pictorial representation, for in his earlier descriptions of the royal galleries of Vienna which he visited, though tolerantly appreciative of their baroque glories in painting and sculpture, it is the more austere engravings of Durer that fixed his attention. How profoundly so is evident when at a later point, in describing the troubled conditions in Bavaria, he describes the city of Nuremberg in words that have a familiar sound:

I have remarked, in Holland and in Prussia, people recovering from political slavery . . . but, in Nuremberg, for the first time, I saw the recent effects of political annihilation. . . . I can truly say, that . . . I never hear a complaint uttered with an open voice; for persons



FIG. 1. A View of the Fortress of Buda and a Part of Pesth, taken from the Observatory.

who would each relate facts when alone with me, would utter but distant insinuations when they were together, so much did suspicion and fear occupy their minds.

Bright is, however, optimistic for the future and when as a symbol of the past glories of liberties that must return he cites the city of Nuremberg, it is exemplified not by its Kings and Conquerors but by its artist-citizen, Albert Durer:

But let political events pursue their course . . . the birthplace of Albert Durer and the scene of his last days will be identified with . . . this once powerful and free city and will serve as a monument to the father of the arts, whose industry and genius were such, that it is to be doubted whether . . . in correctness of drawing . . . he has yet ever been surpassed. (And Bright closes with a full-page reproduction of his epitaph) —“Vixit Germanie decus.”

The View from the Observatory (Fig. 1) with its play of light and shade, that recalls in more moderated tones the Toledo of El Greco, which Bright could never have seen, can be compared to the visions he saw and put down in his verbal description:

A stone rolling from the ruin, and plunging into the abyss below, startled, or I may say awoke me; I beheld in this ruined wall, the fearful battery which once thundred to lay waste the city; I imagined I saw these beautiful vallies and plains bestrewed with the bodies of the thousands who had fallen, still wet with the blood of heroes; the Danube, from whose wave the rays of the setting sun were reflected, appeared reddened with blood; I beheld the city burst into flames, and the exultation of the rejoicing citizens appeared to me the triumphal cry of the victor. The picture of ages which have passed!

All this, though an excellent example of its kind, is clearly more the romanticism of the time and the prevailing literary style of the period than it is the calm voice of Richard Bright, for there follows immediately the recollection of

an impression which had survived the four years that preceded its writing, an incident so simple, even trivial, that not many young men would have recalled it:

As I returned across the bridge towards Pesth, the footpath, which is separated from the carriage-road by a railing, was obstructed by an aged man and woman, who were supporting each other in their tottering steps. A little girl, about ten years old, who stood before me, looked back and exclaimed, with a simple smile, "That is old indeed."—"How old are they, my little girl?"—"Oh, Sir, the woman is a hundred and ten, and the man is nearly a hundred, —I hope I shall never be so old."—"To what age then do you wish to live?"—"Not past thirty, Sir." It was the innocent answer of one who had not yet learnt to appreciate the shortness of years which are gone by.

The episode is put to use in a following short discussion of the longevity of the Hungarians, but it is clearly the remembrance of the antithesis of childhood and old age that had impressed the incident on the young man's mind.

It is love of his fellow man, not only in the abstractions of the human spirit and its works, but in the particularization of these aspects in living persons to which young Bright responds; and the greater is that response in its generosity if the objects of his sympathetic consideration are the lowly and poor in spirit who need affection. Thus, his caustic criticism of the domestic prisons he found as an established custom in each princely estate; yet here his fairness is evident when he admits their horrors to be no greater than those of the jails of his native city, and then again in his subsequently written foreword, when he corrects his textual comments by citing information more recently received of an amelioration of penal conditions in Bristol.

As another example: in his travels through the countryside he meets bands of gypsies. He is fascinated not so much by the picturesque quality of these rovers as by the independent tenacity with which this alien people has maintained for generations its ways of life intact in the midst of a hostile environment.¹ Their origin, their music (cf. tail piece) their familial habits, their somewhat individual ethical viewpoint, are all analysed. In regard to the latter:

For my own part, I have not been able to discover all those marks of natural and inherent depravity in the gypsy character which have been so obvious to others. . . . I am confident that we are apt to appreciate, much too lightly, the actual happiness enjoyed by this class of people, who, beneath their ragged tents, in the pure air of the heath, may well excite the envy of the majority of the poor . . . in the unwholesome haunts of the town. . . . In all attempts to change their habits and to reduce their enjoyments to our standard of happiness, we should carefully bear in mind, that the gypsies are a distinct and separate people and that it is their misfortune rather than their fault to have wandered into a country where property is so strictly appropriated as in Europe. . . . The tide of prejudice which ever flows against them distresses and overwhelms many unjustly, I have no doubt. . . . I must not, however, enter more widely into this subject.

But he cannot let a subject pass until he has exhausted its intellectual content and there then follows 16 quarto pages and an appendix of 28 in which he analyses

¹ Cf. the closing lines of Dvořák's *Zigeunermelodien*, Op. 55, No. 7;
Hat Natur, Zigeuner, etwas dir gegeben?
Ja: zur Freiheit schuf Sie mir das ganze Leben!

in an extensive vocabulary their language as recorded by him in Hungary and on his return home in England and by correspondence with a friend in Spain.

This brief survey of a remarkable book is far from adequate to allow one to draw a formal portrait of young Bright; if the reader's attention has been directed to the source of the necessary material for such delineation its purpose has been accomplished.

Certain distinctive features of the young man's mind stand out, however, with obvious clarity; Richard Bright at 25 is an extraordinarily well balanced individual, with great talents of observation and analysis; the two operations of a questing mind are, in fact, never separated when he is confronted by some new experience. He is also blessed with the ability of articulate expression, both graphic and literary. Dispassionate, yet he shows a generosity and liberality in his enthusiasms that leads one to wonder if perhaps the cool austerity of his outward presence² was not a carefully contrived defence from emotional stresses which arose from a sensitive spirit in contact with a world of too many pleasures and too much pain. For no matter how profound the erudition of his analyses or how gradiloquent his description of worldly pomps and splendours, there always follows some anecdotal evidence of his affection for the simple folk he meets; evidences of a love of humanity ever increasing with the need for this saving grace.

That he was to become the greatest physician of his time and come down to us with a repute that goes far beyond the eponymic fame by which he is daily recalled, is apparent in this "journeying youth" of whom indeed it can be said,

"Heureux, qui comme Ulysse, a fait un beau voyage."

REFERENCE

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² Cf. Garrison (1, p. 182) who cites a contemporary description of Bright as "a heavy, conceited person"!



Concert performed by the Cygani of Sagh.

NEW HORIZONS IN FLUORESCENCE MICROSCOPY¹

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Although fluorescence microscopy is a little over fifty years old, the information accumulated from its application to biology and medicine is still relatively meager. Both the difficulties in working with the physical apparatus and the limited varieties of specific staining techniques have delayed its widespread application.

Recently, however, there has been a renewed interest in fluorescence microscopy as evidenced by the increasing number of investigations employing this technique. Better designed and simplified light sources have become available and have diminished the problems involved in setting up a fluorescence microscope. New fluorescent histochemical reagents have been developed and begin to provide the desired complement to the simpler acidic and basic fluorescent stains. These improvements are largely due to the cooperation of the biologist with the physical scientist. However, the chemist and the physicist cannot aid the biologist if the latter is not sufficiently familiar with these cognate disciplines to be able to describe his physical and chemical problems to those who can solve them. This is particularly true in fluorescence microscopy. The application of fluorescent techniques to problems hitherto without solution attests to the success of the biologist in communicating with and understanding the physical scientist. With these considerations in mind we shall present what we consider to be some of the salient characteristics which point up the potentialities of fluorescence microscopy.

Both classical light microscopy and fluorescence microscopy depend upon the interaction of radiant energy with dye molecules attached to tissues. In both instances a portion of the radiation is absorbed. In the case of classical light microscopy, the radiation is in the form of visible light, and the unabsorbed portion of the spectrum constitutes the color seen in the image of the specimen. In fluorescence microscopy, on the other hand, radiation in the ultraviolet and the violet and blue parts of the spectrum is commonly employed. The unabsorbed portion of the spectrum is not utilized. Rather, the conversion of the absorbed radiation by the fluorescent molecule into radiation of visible wavelengths is the source of the light seen in the image.

The preceding explanation can be restated in a more precise form as follows: a photon passing through the volume occupied by a molecule can be absorbed. If there is a high probability of absorption, the substance is highly colored and is said to have a high extinction coefficient. Absorption of a photon raises the

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³ Fellow of the Dazian Foundation for Medical Research.

molecule to a relatively unstable excited state. In the usual course of events the excited molecule transfers most of the excitation energy to the environment by non-radiative transitions, that is, by collisions with neighboring molecules. In the case of highly fluorescent substances, however, the most probable event is the direct return of the molecule to the ground state, with the emission of secondary radiation. The higher the probability that an excited molecule will return to its ground state directly, the higher is its fluorescent efficiency. In the limit, if all the excitation states decay by emission in an energy range equal to or somewhat less than the excitation energy, the fluorescent efficiency is equal to 1. It happens that many compounds with high fluorescent efficiencies, in the range of 0.1 to 0.9, also have high extinction coefficients.

SENSITIVITY OF ABSORPTION TECHNIQUES

In general, the most highly colored dyes can be detected visually or spectrophotometrically at concentrations of the order of 0.1 microgram per cc for a 1 cm light path through the solution. It can be shown that such a dye can be visualized under the microscope at a concentration of approximately 10^{-15} grams per square micron; or, assuming a molecular weight of approximately 300, about one million molecules per square micron can be detected. By ordinary macrochemical standards, this represents extremely high sensitivity. From the histochemical point of view, however, it is somewhat disheartening: although, in the limit, one can detect 10^{-15} grams of a substance per square micron, this is equal to about 0.1 % concentration in a cubic micron, and all but a few of the substances in cells are present at concentrations considerably lower than 0.1 % of the wet weight. Therefore, even with colored reagents or colored end products which have extinction coefficients comparable to those of the most highly colored dyes, the cytochemist is restricted to the study of the major components of the cells, that is, proteins, nucleic acids, polysaccharides, and lipids. He cannot hope to study with ordinary histochemical stains the detailed distribution among the cell organelles of the multitude of compounds and side chains of the major components which exist in concentrations below about 0.1 %.

The sensitivity of the absorption technique is limited by two factors: a) the degree of reduction in intensity of the light beam as a result of absorption by the molecules in the light path; and b) the smallest difference in light intensity which can be detected visually with confidence or measured with accuracy. This limit is usually *not set by the sensitivity of the eye or photometer*, since it is almost *independent of the actual light intensity* at which the observations or measurements are made. However, at extremely high intensities the linearity of response of the eye and photocell drops rapidly, and at extremely low intensities, the ability to detect and discriminate is seriously limited by statistical, electrical and thermal "noise" (1).

It is generally agreed that about a 5% difference in intensity or brightness represents a practical limit to visual contrast acuity, and this also represents the limit to which reasonably accurate measurements can be made easily with a photometer.

SENSITIVITY OF FLUORESCENCE TECHNIQUES

The emitted light of a fluorescent substance is in general of lower energy, and therefore of longer wavelength, than the exciting radiation. If, by optical filtering, a fluorescent substance is exposed to radiation only of wavelengths equal to or shorter than those which are strongly absorbed; and if a second filter, placed between the fluorescent substance and the eye or photometer, passes only wavelengths longer than those which are strongly absorbed, then only the fluorescent radiation will be observed. The amount of fluorescent light that can be detected in such a system is proportional to both the intensity of the light incident on the fluorescent substance and the sensitivity of the eye or photometer. In the ideal case the background is absolutely dark and the contrast which the eye or photocell sees is infinite and independent of the intensity. Therefore, theoretical limit of sensitivity for fluorescence, in contrast

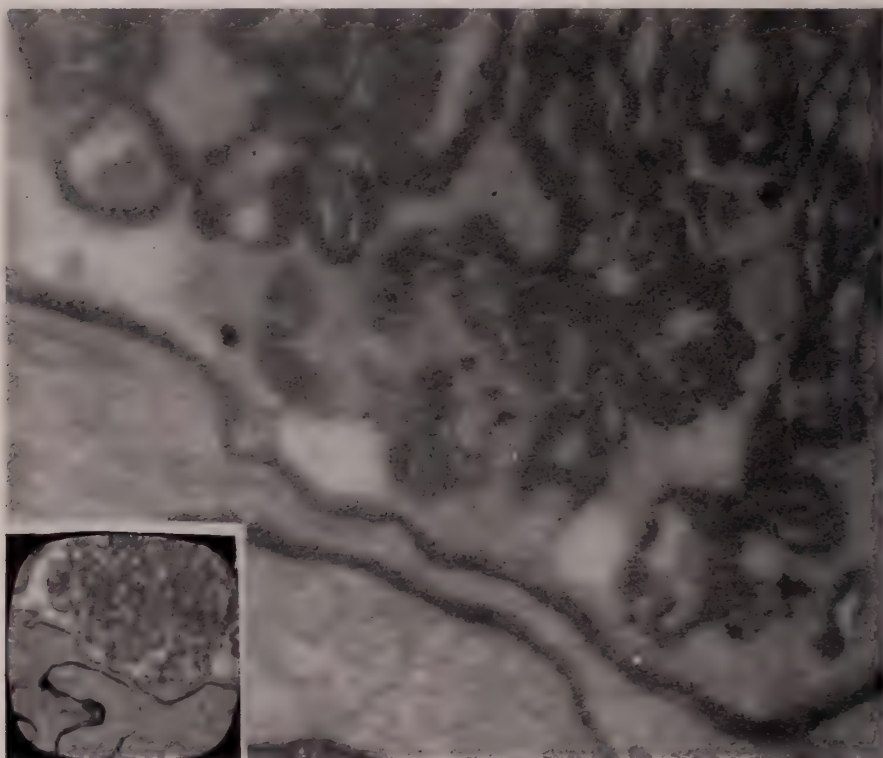


FIG. 1a

FIG. 1. PAAS reaction on $0.5\ \mu$ section of human kidney with glomerulonephritis showing parts of a glomerulus and an adjacent tubule, $1250\times$. a) Absorption image photographed with blue light (ca. $435\ m\mu$). b) Medium dark phase contrast image photographed with green light (ca. $546\ m\mu$). c) Fluorescent image-photographed with "crossed" filters. Note that the glomerular basement membranes appear thickened and uniformly stained in Fig. 1a, but are resolved into two components, a thin highly fluorescent layer adjacent to the capillary lumen, and thicker, less fluorescent deposits on the epithelial side, in Fig. 1c. This detail is not resolved by phase contrast in Fig. 1b. The erythrocytes in the lumina of the capillaries absorb blue light (Fig. 1a) but do not fluoresce appreciably (Fig. 1c).

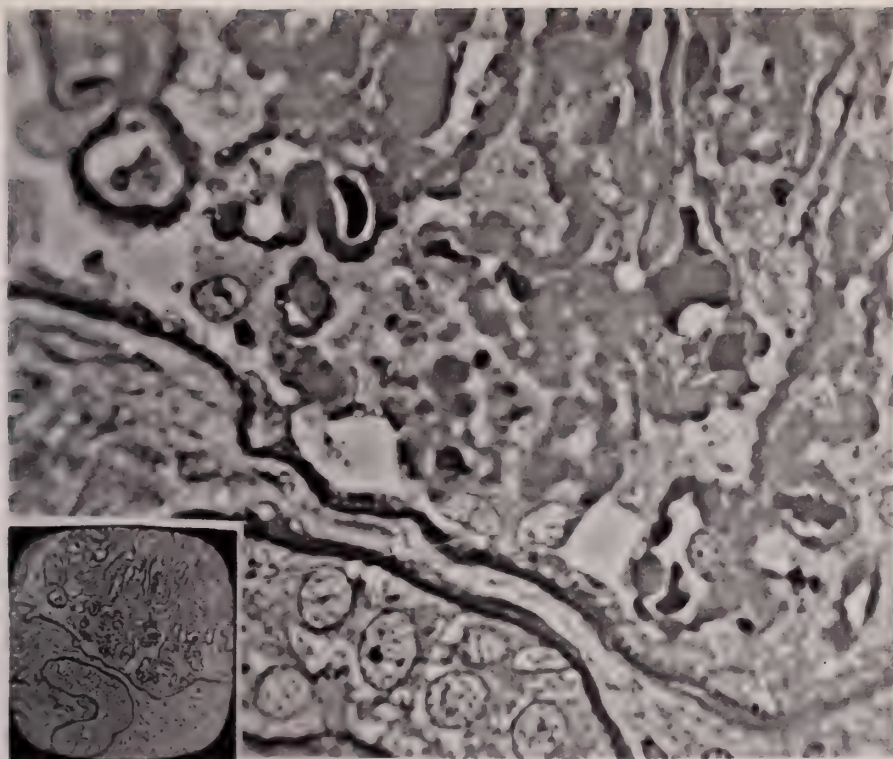


FIG. 1b

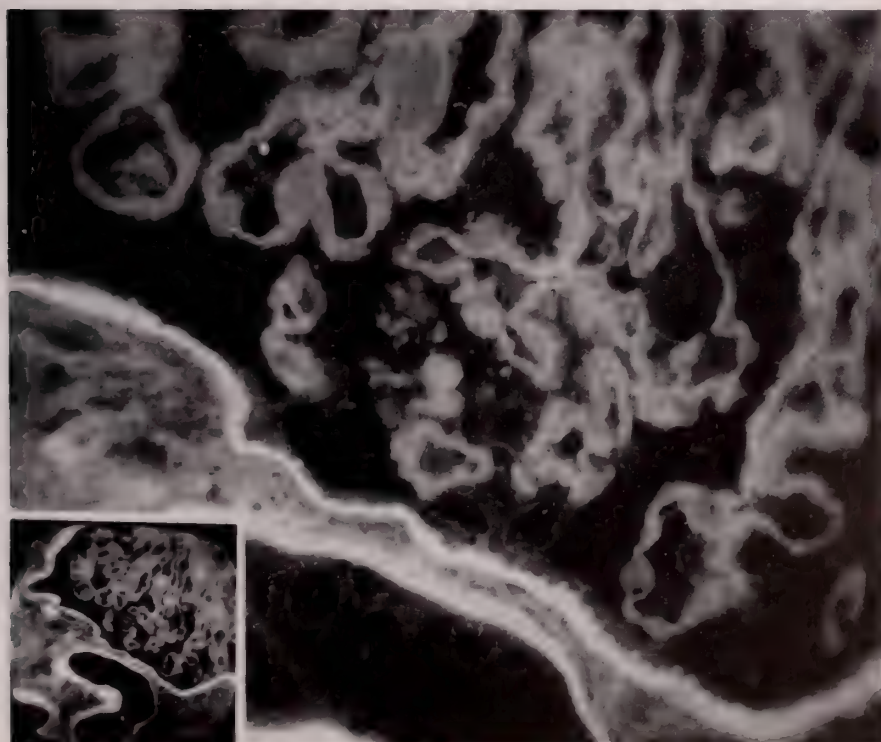


FIG. 1c

to that of absorption analysis, depends directly on both the intensity of the illumination and the sensitivity of the eye or photocell.

The level of sensitivity in practice depends directly upon the adequacy of the filter system, the intensity of the available light sources, and the fluorescent efficiency of the dyes.

a) *Filter System.* Since the eye is most sensitive to wavelengths in the region 500–555 $m\mu$, it is desirable to work with substances which fluoresce in this region. It happens that it is possible to "split" the visible spectrum "both ways" most easily at about 500 $m\mu$. That is, excellent filters exist which will remove all radiations longer than 480 $m\mu$ from a beam of light with minimal attenuation at shorter wavelengths, as well as filters which remove all light of wavelengths shorter than 500 $m\mu$ with minimal attenuation of longer wavelengths. A combination of such filters is absolutely opaque to visible light.

b) *Light Sources.* The most intense sources of radiation available for laboratory use are the compact high pressure arc lamps and the high current carbon arc. In average brightness they fall within an order of magnitude of one another (2), but on the basis of the blue, violet, and ultra-violet output, the high pressure arcs, particularly the super high pressure mercury arcs, hold a decided advantage. The mercury spectrum between 312⁴ and 480 $m\mu$ consists of a number of strong emission lines. The strongest line in this spectrum, on a quantum rather than an energy basis, is the one at 435.8 $m\mu$, next strongest the cluster of three at about 365 $m\mu$. These, with the 404 and 407 lines, constitute the bulk of the radiation output of the high pressure mercury arc within this portion of the spectrum.

c) *Fluorescent Dyes.* Among the vast number of fluorescent substances there are two families of dyes which are well suited to the above mentioned light source and filtering system. These dyes are derivatives of the acridine and xanthene families, the best known members of which are Acriflavine and Fluorescein, respectively. These dyes are characterized not only by very high extinction coefficients, but also by fluorescent efficiencies in the range of 0.1 to 0.9. Since the absorption spectra of these fluorochromes have peaks with half-widths of about 50 $m\mu$, the very best we might hope to find is a compound among them with an absorption peak at about 435 $m\mu$, and an emission peak between 500 $m\mu$ and 555 $m\mu$. Acriflavine, with its absorption peak at about 460 $m\mu$, and its emission peaked at about 527 $m\mu$, conforms reasonably well to these requirements.

Theoretical limits of sensitivity of the model fluorescence system. If one arranges an Osram HBO 500 mercury arc to fill the full aperture⁵ of an N.A. 1.4 immersion condenser, the illuminance in the specimen plane of the microscope can be made roughly equal to the radiance of the arc stream itself. The HBO 500, operated at 7.5 amperes, emits about 2×10^{15} photons at 435.8 $m\mu$ per mm^2 of arc stream per second.⁶ Thus, up to 10^{12} photons (435.8 $m\mu$) can pass through one square micron in the specimen plane per second.

⁴ We will disregard the group below 312 $m\mu$ since they are not transmitted by glass.

⁵ As opposed to the fractional aperture of a darkfield condenser.

⁶ With the intensity distribution of a point source.

The molecular absorption cross-section (2.3 times the molecular extinction coefficient) of Acriflavine at 435.8 $m\mu$ is about $1.4 \times 10^{-8} \mu^2$. Therefore, one molecule of Acriflavine with a fluorescent efficiency of 0.5, placed in the specimen plane of the microscope in the model system would emit 7×10^3 photons per second. An N.A. 1.3 immersion objective can collect almost one-half of these, that is, about 3000 photons per second.

The lower limit of sensitivity of the dark adapted eye to green light is approximately 150 photons per second (3). Therefore, in such a system we would have a sensitivity about 20 times better than that needed to detect a single molecule of Acriflavine visually!

Practical limits of sensitivity of fluorescence systems. In practice we fall far short of this level of sensitivity. The very best "crossed" filter systems transmit as little as 30% of the 435.8 $m\mu$ line and as little as 30% of the green fluorescence of Acriflavine. The optical system transmits as little as 40% of the light because of absorption, reflection losses and lens aberration. At this point the practical system is about one-twentieth as efficient as the model system, that is 150 photons per second would be delivered to the eye for every molecule of Acriflavine. Further limitations are imposed by the fluorescence of the lenses, filters, microscope slide and cover glass, and specimen autofluorescence. By preparing special condenser and objective immersion "oils" as the light filters of the system, fluorescence of the condenser is filtered out and fluorescence of the objective is prevented. Proper choice of filter substances circumvents the problem of filter fluorescence. What remains is the fluorescence of the slide, cover glass and mounting medium and this constitutes the background fluorescence. The autofluorescence of a tissue section, particularly after prolonged formalin fixation, may be ten to one hundred times higher than this background. Chemical treatment (see below) usually can reduce the autofluorescence to near the background value. It can be shown that this value is approximately 1.4×10^4 photons μ^2 sec. collected by the objective in the visible part of the spectrum. At such low levels of light intensity, discrimination by photopic vision requires about a 50% difference in light intensities. Therefore, one square micron must contain approximately 100 molecules of Acriflavine before the fluorescence of the dye can be discriminated from the background fluorescence.

Comparing the minimal concentration of dye necessary for detection in an absorption system to that of a fluorescence system it is seen that the fluorescence system is more sensitive than the absorption system by a factor of about 10^4 .

Potential limits of sensitivity of fluorescence systems. The calculations to this point have been on the conservative side. Light sources five times as bright as the HBO 500 are available. By mounting a specimen on a cover glass rather than a slide the background fluorescence drops by about a factor of 5. We have reason to believe that specially prepared non-fluorescent glass slides and cover slips better by a factor of 100 can be prepared. Thus it is entirely possible that in the near future one will be able to localize a single molecule of a compound like Acriflavine in a histologic or cytologic preparation. At present, the sensitivity of 100 molecules μ^2 of specimen in itself represent great analytic potential for the microscopist.

APPLICATIONS OF FLUORESCENCE MICROSCOPY

Coons, et al. (4, 5) in their brilliant work on Fluorescein-tagged antibody, introduced Fluorescein isocyanate as a reagent for certain side groups of proteins. Isocyanates react readily with NH_2 , SH and phenolic OH groups. This concept of a specific fluorescent histochemical reagent directly stimulated most of the work in this communication. Their approach of tagging a highly specific antibody and of using this conjugate as a reagent is now well known and is receiving increased application throughout the fields of biological microscopy.

Fluorescein and its derivatives possess about one-fourth the sensitivity of Acriflavine in a system with the light source and filters mentioned above, because their absorption maxima (ca 495 $\text{m}\mu$) are even further removed from 435 $\text{m}\mu$ than that of Acriflavine. Nonetheless, such a system is superior to any other with which the authors are familiar for detecting traces of Fluorescein isocyanate-protein conjugates in microscopic preparations.

It would be desirable to synthesize acridine derivatives with absorption maxima closer to 435 $\text{m}\mu$ which could be used in a manner analogous to that of Fluorescein isocyanate. Diazonium salts would be especially desirable for the production of fluorescent conjugates. (The conjugates of the diazonium salt of amino fluorescein, the parent compound of Fluorescein isocyanate, do not fluoresce.) (6) These problems are being investigated in our laboratory.

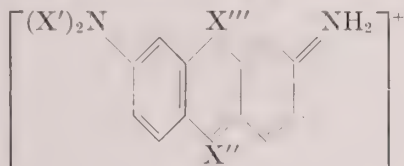
From the quantitative point of view, fluorescence cytophotometry holds considerable promise. At sufficiently low concentrations, the number of quanta emitted from an area of a preparation is directly proportional to the amount of fluorescent substance and *independent of the distribution* of that substance within the area (7). This permits a straightforward photometric approach to quantitative analysis. However, the immediate environment of the fluorescent molecule can easily alter the fluorescent efficiency and this represents the greatest hazard to the quantitative approach.

Perhaps the greatest gains that will be made by fluorescence microscopy in the near future will be at the structural level in pathologic research. In the past few years there has been an increasing turn to the use of thin sections (0.5 to 2 μ) for the light microscope, especially stimulated by the recent advances in microtomy that have accompanied the growth of biological electron microscopy (8). Study of structure in thin sections permits one to avoid the confusion of overlap and thereby permits more certain interpretation of spatial relationships (9). The use of thin sections is not without sacrifice. The reduction in optical path through the section diminishes the contrast in stained specimens. Thus a large part of the potential gain in structural analysis is lost. Phase contrast analysis in part compensates for this loss (10), but it does not easily permit the kind of chemical discrimination that stains and histochemical reagents provide. Insofar as it is possible to synthesize specific fluorescent analogues of histochemical reagents, the contrast loss inherent in thin sections need no longer limit the potentials of thin sections.

The remainder of this communication is devoted to a study of the preparation and one application of such a fluorescent analogue. We hope to illustrate both the potentials and the pitfalls of this approach.

THE PERIODIC ACID ACRIFLAVINE-SCHIFF REACTION (THE PAAS REACTION)

In 1948 it was reported (11) that a few basic dyes other than Pararosanilin (Basic Fuchsin) could be used to prepare a Schiff-like reagent for aldehydes, particular attention being paid to their application in the Feulgen nucleal reaction. This phenomenon was investigated (12) and it was discovered that an N-sulphinic acid Schiff-type aldehyde reagent could be prepared from compounds which can form one of the following cationic structures:



Where $X' = \text{H}$ or R ; and R is an alkyl or aryl group.

Group (I) When $X'' = \text{CH}$ or CR and X''' is absent: (Diphenylmethane and triphenylmethane derivatives)

(II) When $X'' = \text{CH}$ or CR , $X''' = \text{NH}$ or NR (Acridine derivatives)

(III) When $X'' = \text{CH}$ or CR , $X''' = \text{O}$ (Xanthene derivatives)

(IV) When $X'' = \text{N}$, $X''' = \text{NH}$ or NR (Azine derivatives)

(V) When $X'' = \text{N}$, $X''' = \text{O}$ (Oxazine derivatives)

(VI) When $X'' = \text{N}$, $X''' = \text{S}$ (Thiazine derivatives)

Most of these Schiff analogues differ from the classical reagent in apparently being unable to form a colorless solution, and are therefore useless as analytical aldehyde reagents in organic chemistry. The absence of the colorless form, however, is not a disadvantage in their application to insoluble sections and smears, since the unreacted excess of the reagent is routinely washed away.

In all members of the series, the distribution of the Schiff analogue reaction product and the classical Schiff reaction product as viewed under the ordinary light microscope after periodic acid oxidation and the Feulgen hydrolysis were identical. Controls were identical to one another.

The classical Schiff reagent is prepared with Basic Fuchsin (group I) (13). Azure A (group VI) has now been used quite extensively in the Feulgen reaction in microbiology (14) and cytology (15) as a result of this study. Acriflavine (group II) can also be used in the preparation of a Schiff-like reagent. The reaction product of this reagent with aldehyde has an absorption and fluorescent spectrum quite similar to that of Acriflavine itself. We are thereby provided with a fluorescent analogue of a tool which holds an important position in histo- and cytochemistry.

MATERIALS AND METHODS

*Apparatus**(1) Light source.*

A 500 Watt Osram super-high pressure mercury arc HBO 500⁷ was used as the light source for the microscope. It was operated at approximately 7.5 am-

⁷ Obtainable from Unex Prod. Corp., New York, N. Y.

peres from a 110 v. D.C. line source in series with approximately 6 ohms ballast resistance (about one-half of the nichrome wire of a standard 1000 watt ceramic infra-red heating element). The starting high voltage spark may be supplied by a photoflash trigger transformer (e.g. United Transformer Co. PF-3) in a conventional starting circuit. An f 4.5 achromatic doublet was placed so that the are was in the first focal plane of the lens.

(2) *Microscope.*

A Leitz Labolux microscope equipped with an N.A. 1.4 achromatic condenser and $90\times$ N.A. 1.25 Zeiss (Jena) achromatic medium dark contrast phase objective and with a binocular-monocular photographic body tube (oiyeesine-modified for the Labolux) with $8\times$ periplan oculars was used. For phase microscopy an appropriate phase condenser was substituted.

(3) *Filters.*

(a) A 1 cm. path of saturated CuSO_4 in 0.1 N H_2SO_4 was used between the light source and the microscope to remove the infrared and red part of the spectrum which are transmitted by the "crossed" filters described below.

(b) Objective immersion filter: 6.5 grams of crystalline phenol are dissolved in 3.9 ml. of glycerol. This solution is saturated with Naphtho. Yellow S (C.I. 10) at 100°C ., cooled to room temperature and after 4 hours is centrifuged to free the supernatant of dye crystals. This solution has a refractive index of about 1.515 and will not harm the metal, glass or cement of the objective.

(c) Condenser immersion filter: Crystal violet (C.I. 681) is dissolved in glycerol. The concentration used here depends upon the working distance of the condenser.⁴

(d) For absorption microscopy, only the Copper Sulfate and Crystal Violet filters were used. The objective immersion filter was replaced by colorless immersion oil, refractive index 1.515.

⁴ This may be adjusted for each microscope in the following manner: A line is drawn across the middle of a plain glass microscope slide with India ink. This slide is "immersed to" the microscope condenser with a solution of Crystal Violet in glycerol. The ink line is brought to the middle of the field, and a drop of the objective immersion filter is placed on the top of the slide over the line. The immersion objective (carefully cleaned of all ordinary immersion oil) is immersed and focussed on the edge of the ink line. The condenser is focussed to bring the image of the source in the plane of the line. This will be a bright red image. The CuSO_4 filter is now placed between the microscope and the light source. If the concentration of the Crystal Violet is too low, the field will appear bright to dull blue-green; if too high, an extremely faint gray-green fluorescent image of the light source will appear against a totally black background. In the latter case, the condenser is racked upward, and as the path through the condenser filter is shortened, more and more exciting radiation enters the glass of the slide. This causes either an increase in the fluorescence of the glass or keeps it at about the same level—even though the cross section of the beam is increasing. Beyond this, blue-green light finally begins to pass through the system. The concentrated solution must then be diluted with glycerol until, with the condenser focussed a dull gray-green image of the source can be visualized which grows slightly weaker on racking the condenser upward (just before it begins to pass blue-green light).

(e) For phase microscopy a Wratten 74 filter may be used.

Reagents

(1) Osmium tetroxide solution

- 1 gram OsO_4
- 50 ml distilled water
- 10 drops of M/15 phosphate buffer pH 7.4

This reagent remains stable for months if it is made up in chemically clean glassware and is kept well stoppered in the refrigerator.

(2) Periodic Acid solution

- 400 mg Periodic Acid
- 45 ml distilled water
- 5 ml M/5 sodium acetate

(3) Acriflavine-Schiff solution

- 250 mg Acriflavine Dihydrochloride
- 500 mg $\text{K}_2\text{S}_2\text{O}_8$
- 50 ml 0.1 N HCl

This solution must be kept in a well stoppered container to prevent excessive loss of SO_2 (as is also the case for the classical Schiff reagent). The solution is usable as long as the pH remains between 1.25 and 2.4, and it smells strongly of SO_2 .

Procedure

A portion of a surgically removed formalin fixed human kidney⁹ was postfixed for four hours in the osmium tetroxide solution. The tissue was dehydrated in alcohol, embedded in 5% methyl, 95% butyl methacrylate and sectioned on an ultramicrotome at a thickness of 0.5 microns (8). The methacrylate was removed with CCl_4 and the sections were brought to water. They were then treated for 5 minutes at room temperature in the Periodic Acid solution. The slides were washed in running water and placed in the Acriflavine-Schiff solution for 20 minutes. They were again washed in water and passed through two solutions of acid alcohol for ten minutes each¹⁰, and following dehydration were mounted in mineral oil (refractive index 1.46).

A variety of formalin and Carnoy fixed human and animal kidneys were embedded in paraffin and sectioned at 4 μ . The staining technique was identical to that used for thin sections except for a 10 minute treatment in the osmium

⁹ Kindly provided by Dr. Jacob Churg.

¹⁰ The substitution of a water wash in place of the customary thiosulfate rinse, and of acid alcohol for the sulfite baths or other rinses yielded essentially identical results, both in case of the classical PAS and the PA-AS reactions. The acid alcohol was more effective than the sulfite in removing unreacted reagents; this is easily demonstrated with the PAAS preparations because small concentrations of unreacted reagent are readily detected.

tetroxide solution following Periodic Acid oxidation. The sections were washed in water for one minute both before and after the OsO_4 treatment.

RESULTS

When examined by absorption microscopy, the distribution of the dye was identical to that in the standard PAS preparation. In the thin sections, basement membranes fluoresced orange to yellow-orange. Connective tissue fibers were green. The cytoplasm was faint green with occasional bright yellow-orange granules in tubular cells. The nuclei were faint green or non-fluorescent. Pathologic examination of this kidney showed glomerulonephritis. The glomeruli showed thin, intensely fluorescing yellow basement membranes. Along the epithelial surface of these membranes were numerous deposits of less intensely fluorescing homogeneous material several times as thick as the basement membrane proper. The basement membranes of the glomerular capsules were intensely fluorescent, and sometimes revealed short comb-tooth projections extending into the capsular space (Fig. 1. c).

Thick ($4\ \mu$) sections showed a considerably higher intensity of fluorescence, roughly proportional to the increase in thickness. Basement membranes were bright orange to yellow-orange; connective tissue fibers were bright green; cytoplasm was green with yellow-orange granules in tubular cells. The brush borders of the proximal tubules were reddish-orange. Nuclei were faint to moderately bright green.

Unstained, untreated control sections showed green autofluorescence which was particularly intense in the connective tissue fibers and in the elastica of the blood vessels, fainter in the cytoplasm, and very faint in the nuclei. Yellow and orange fluorescence of the kind found in stained specimens was absent.

Unstained sections treated with OsO_4 showed a marked diminution of autofluorescence in most of these sites. Except for elastica, the remaining tissue elements showed an extremely faint green fluorescence.

OsO_4 treated sections placed in the Acriflavine-Schiff reagent without periodic acid oxidation showed a considerably more intense green fluorescence of nuclei, cytoplasm, and connective tissue elements than sections treated with OsO_4 alone. No yellow or orange fluorescence was present.

Sections treated for 1 hour in 50% acetic anhydride in pyridine at 100°C before the PAAS procedure showed a marked reduction of staining in the basement membranes, cytoplasmic granules and brush border, and a slight reduction in the connective tissue fibers, cytoplasm, and nuclei as contrasted to the unacetylated, PAAS treated preparation. The basement membranes fluoresced green and could not be readily distinguished from the surrounding connective tissue fibers.

DISCUSSION

Comparison of the absorption images of the PAS and PAAS preparations discloses identical distributions, and leads one to conclude that at this level of sensitivity these reagents are histochemically equivalent for all practical pur-

poses. Comparison of the fluorescence and absorption images, however, reveals fluorescence in a number of sites which are negative by absorption techniques.

The increased sensitivity of the fluorescence technique precludes the use of the absorption images as the point of reference for the determination of the specificity of the fluorescence methods *in these sites*. The fluorescence positive, absorption negative sites may include one or more of the following groups:

- (1) PAS positive material present in concentrations too low to be detected by absorption techniques;
- (2) Trace aldehydes or non-aldehydic substances which react with the Acriflavine-Schiff reagent independent of Periodic Acid oxidation;
- (3) Sites of autofluorescence not eliminated by OsO_4 treatment.

In addition, the purity of the Acriflavine reagent may be an important factor. Fluorescent impurities would be a much greater source of error in fluorescence microscopy than colored impurities would be in absorption microscopy.

Autofluorescence varies in intensity from one preparation to another. In general, it can be markedly reduced or eliminated by use of oxidizing agents such as OsO_4 , KMnO_4 , and others. We find, incidental to our attempt to eliminate autofluorescence, that treatment with OsO_4 immediately prior to staining prevents part of the staining pattern (especially the nuclear staining) of the unoxidized as well as the oxidized sections.

The presence of trace aldehydes and other substances which react with Acriflavine-Schiff reagent independent of the Periodic Acid oxidation is confirmed by the use of an Acriflavine Schiff treated section without previous Periodic Acid oxidation.

Trace quantities of PAS positive substances in sites other than those usually visualized by absorption techniques are confirmed to be present by the comparison of PAAS treated sections to identically treated acetylated controls. It would now be desirable to devise a reaction for blocking the reactive groups remaining in such a control. Such a reaction would have to yield products stable to the conditions for hydrolytic cleavage of the acetylated 1-2 glycol groups, and stable to Periodic Acid oxidation. In such a way it would be possible to develop a more specific, fluorescent PAAS technique.

While both Acriflavine and Acriflavine-Schiff-aldehyde addition products have a green fluorescence in solution, the PAAS treated materials fluoresce in colors varying from orange to yellow to green. It is known that the interaction of closely approximated dye molecules with one another results in metachromatic shifts of their absorption and emission spectra. There is good reason to believe that the color distribution observed is a reflection of the concentration of the reaction product (16, 17). Oxidized polysaccharide substances have a large number of reactive aldehyde groups per unit surface area of the molecule. One would therefore predict that the Acriflavine-Schiff reaction product of such a substance would tend to "crowd" Acriflavine molecules against each other in contrast to non-polysaccharide substances. The red-orange to yellow-orange fluorescence may therefore be tentatively taken to indicate the presence of polysaccharide substances. Some of the yellow and green fluorescent substances may

also prove to fall in this category, but their identification must remain very much in doubt at this time.

The preceding illustration points up the problems of specificity which arise as a result of the increased sensitivity of the fluorescence technique. The gains to be made by this technique justify an effort to surmount these problems. In the future lie such intriguing possibilities as specific enzyme reagents which would be analogues of normal substrates with attached fluorescent side chains. These would form stable complexes with the enzyme *in vivo* or *in vitro*. The site of the enzyme might then be visualized directly in appropriate preparations in the fluorescence microscope.

It has been the purpose of this communication to examine and illustrate some of the potentials of fluorescence microscopy. We believe that the techniques will continue to be improved and simplified, and that efficient, specific reagents can be developed with a modicum of effort. Indeed, we anticipate that fluorescence microscopy will become an essential microscopic tool in the not too distant future.

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A DISCUSSION ON EOSINOPHILIC GRANULOMA OF BONE, LETTERER-SIWE DISEASE AND SCHÜLLER-CHRISTIAN DISEASE

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Because of the characteristics of the clinical and anatomical pictures of Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma of bone, these disease processes were gradually recognized as independent diseases.

However, there developed a peculiar concept that these diseases were basically identical in nature, and they should be classified as one entity, completely disregarding their strikingly different clinical pictures.

Lichtenstein (1), who holds this view, for instance, based upon the microscopic type of cells found in these diseases, emphasizes that the common factor in all three conditions is histiocytosis, thus giving the term histiocytosis X.

As Siwe (2) pointed out, it is an over simplification of the description of the disease processes and may create more confusion in the understanding of these disorders.

In a most recent paper, Schulz (3) stated: "The now widely accepted concept that Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma of bone are different manifestations of the same entity resulted from the accumulation of reports of cases in which features of two or more of these conditions occurred in the same patient, usually a child or young person. The small number of adult cases which have been described under the general term 'non-lipid reticuloendotheliosis' present an even more confusing picture. Many of the cases bear only a slight resemblance, either clinically or pathologically to others in the group."

Whether this concept has been widely accepted or not, the usage of one general term tends to confuse rather than clarify the problem.

This concept appears to be illogical, because the three diseases show entirely different patterns, clinically and anatomically. Yet, many clinicians and pathologists are inclined to accept this view. Perhaps it is because no firm opinion against this concept has been strongly expressed in recent years. Siwe (2) is probably the only one who decidedly rejected this interpretation. It is for this reason that a critical discussion of this disturbing problem will be made here.

It seems that the main cause of this confusion originated in the lack of understanding of these three disorders. I shall, therefore, briefly describe the essential, but fundamental parts of each disease before discussion.

EOSINOPHILIC GRANULOMA OF BONE

Eosinophilic granuloma of bone is a sharply circumscribed destructive process involving usually a solitary bone, or occasionally more than two bones. Localized pain is the only clinical sign; and no systemic symptoms are to be found associ-

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ated with this bony lesion. It is common in young children, but may occasionally be seen even in patients over 50 years of age.

Anatomically, the lesion reveals a sharp destruction of bone, and it appears as a bone abscess. The central portion is filled with necrotic tissue.

Microscopically, the lesion is filled with necrotic cells together with various inflammatory cells including polymorphonuclear leukocytes, plasma cells, and lymphocytes. An accumulation of unique histiocytic cells which sometimes appear so dense as to actually simulate a sarcoma, is a most characteristic cellular element. Of course, there are a striking number of eosinophiles, however, they may not be so numerous in certain instances. Because the necrotizing process exists, it is not surprising to find necrotic cells and a small number of Sudan positive cells which belong to the lipophages. (This should not be confused with foam cells in Schüller-Christian disease).

The follow-up observation of cases of eosinophilic granuloma indicates a benign nature of this disease process. Complete healing is to be expected in all cases, through surgical intervention, radiotherapy or both.

The following two cases are used to demonstrate the characteristics of the osseous lesions:

1. A punched out lesion of the skull (Fig. 1. A.) was found to be present in a 16 year old boy. The lesion developed on the spot which had been hit by a baseball. The biopsy tissue revealed a typical eosinophilic granuloma. Following radiotherapy, the lesion was completely healed. Ten years later the patient was accepted for army duty.

2. A rib lesion of a 10 year old boy, which was previously described by us (4). The lesion was resected in 1939 and no recurrence has been observed to date.

In all cases which I have diagnosed as eosinophilic granuloma of bone, there has been complete healing or no recurrences have been found during many years follow-up observation.

Schairer (5) initially interpreted this type of bone lesion as an osteomyelitis with conspicuous eosinophiles. It is true that the general pattern is that of osteomyelitis or bone abscess. However, the peculiar accumulation of histiocytic cells in addition to eosinophiles, differentiates it from ordinary osteomyelitis.

Carrington and Davison (6) in 1925 reported a case of multiple bone abscesses in various bones in which *B. paratyphoid B* had been recovered. It is unfortunate that no histological description of their cases was recorded. It is interesting to note that the bone lesions healed completely.

In cases of Hodgkin's disease, the number of eosinophiles varies markedly; in some instances there are so few eosinophiles found that we believe that eosinophiles are not an essential cell element of Hodgkin's disease. A similar situation is to be found in eosinophilic granuloma of bone. In certain cases eosinophiles are not striking, but the presence of histiocytic cells makes it a bone granuloma. The most essential cell elements in my opinion, therefore are histiocytic cells and not eosinophiles. However, since the term eosinophilic granuloma of bone has become so well known, perhaps it is proper to continue use of such terminology.

Since the bony lesion is easily healed without a trace of generalized systemic

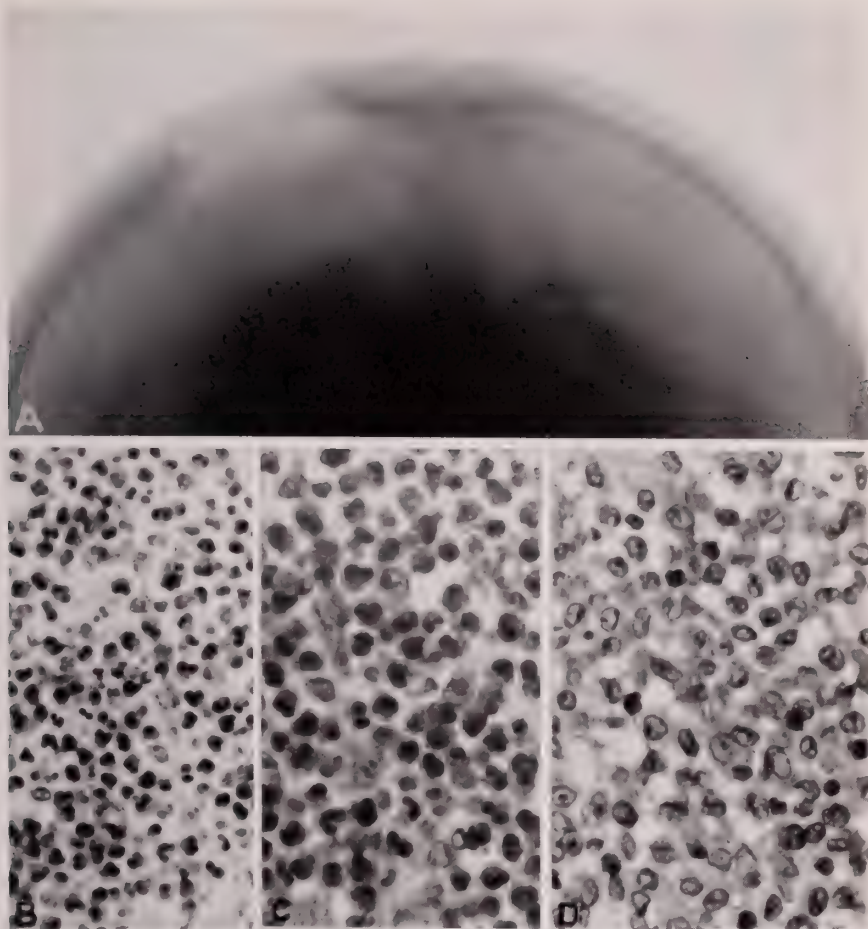


FIG. 1. A. Solitary lesion of eosinophilic granuloma of skull, 16 year old boy. B-D. Microscopic cellular elements of eosinophilic granuloma. Many polymorphonuclear leukocytes (B), Large number of eosinophilic leukocytes (C) and characteristic histiocytic cells (D).

symptoms, and a history of trauma is obtained in some instances, it is natural to look for a focal etiological factor. However, it is inconceivable that mechanical damage to bone alone may create an abscess-like lesion. It may, however, be possible that a traumatic lesion of bone is infected secondarily by some kind of virus, thus creating this unique histiocytic granuloma of bone.

In the past, I have observed cases of *Salmonella* infection occurring in a bone which had been previously damaged by an aortic aneurysm. It is my belief that a damaged tissue may be easily infected, and if an organism has a certain biological characteristic which will bring forth a histiocytic cell response, this may be responsible for the bony granuloma. Trauma and superimposed infection might therefore be an etiological factor.

I am well aware of the fact that papers were published in the past in which this

type of bone lesion and pulmonary granuloma were found simultaneously (7). I have observed one such case. I also have seen a case of eosinophilic granulomatous pulmonary lesions which occurred only in the lungs. Those cases are rather atypical, and I am of the opinion that these types of cases should not be used for a discussion of genesis.

LETTERER-SIWE DISEASE

Letterer-Siwe disease is an acute extremely toxic systemic disease mainly affecting the young infant, and always fatal within a short time. Because of improved therapeutic measures in recent years the clinical course may be prolonged to a certain extent. Cases usually start with high fever and cutaneous hemorrhages; lymphadenopathy and marked hepato-splenomegaly soon become apparent, followed by severe anemia.

At autopsy, one finds in addition to skin hemorrhage, marked hepatosplenomegaly and generalized enlargement of all lymph nodes. The latter, particularly along the intestine and mesentery, show a marked red appearance (Fig. 2).

Microscopically, one finds a scattered accumulation of histiocytic cells in various organs, particularly in hematopoietic organs, such as lymph nodes, bones, liver, spleen and mucosa of the intestines. Because of the acute toxic condition, it is natural to find tissue necrosis, and consequently one finds focal necrosis. This may be why in certain cases one observes fat containing cells, or lipophages.

This unique clinical and anatomical picture, described above, was an exact description recorded in the original paper by Letterer in 1926 (8). No bony lesion was found in his case.

In 1933, Siwe reported an identical case, however, with a cystic lesion of the fibula. Although Siwe published this as a reticuloendotheliosis, thereby naming a new disease process, several identical cases had been recorded before Siwe's paper.

The reports of Letterer and Siwe may perhaps have been the best detailed description of this unique condition. It has been identified as Letterer-Siwe disease.

The four cases we have observed, were exactly identical with the original case of Letterer in every respect. No bony lesions were found in our cases.

It was perhaps unfortunate that Siwe's case showed one cystic bone lesion. This bony lesion became a source of confusion. The description of his pathologist, Sjoevall indicates that this bony lesion was most probably a subacute bone abscess. Its cyst wall was fibrosing. In my opinion, this was probably a recent bone abscess, which is related to the septic general condition.

However, later, cases with multiple bone lesions which may well be simple multiple bone abscesses, as Carrington and Davison's case, have erroneously been regarded as Letterer-Siwe disease. If this type of disorder were named Letterer's disease, instead of Letterer-Siwe disease, this late confusion might have been avoided.

In this group of cases, an abscess-like necrosis of thymic tissue has been reported. In my series, too, I have found considerable acute necrosis in the thymus



FIG. 2. Characteristic macroscopic lesions of Letterer-Siwe disease. Cutaneous hemorrhages (A and B). Marked hepatosplenomegaly. Distended stomach showing multiple hemorrhages (C). Diffuse enlargement of lymph nodes along the colon. Note hemorrhagic appearance of lymph nodes (D).

and many lymph nodes. None of the bones in our cases revealed necrotic areas. However, it is reasonable to expect certain necrotic areas, as found in lymph nodes.

This unique form of disorder has been interpreted by Letterer, Akiba and others to be of an acute infectious nature, although no organisms were found. From the clinical course and anatomical picture it is quite natural to consider this condition as one type of acute sepsis. The only difference from the ordinary sepsis is that of the presence of histiocytic cells. An etiological agent might be a very virulent virus, which gives a unique cellular response, because repeated bacteriological examinations have been completely negative.

It is for this reason that this malady should be called an acute infectious reticuloendotheliosis as an anatomical expression, instead of a non-lipid reticu-

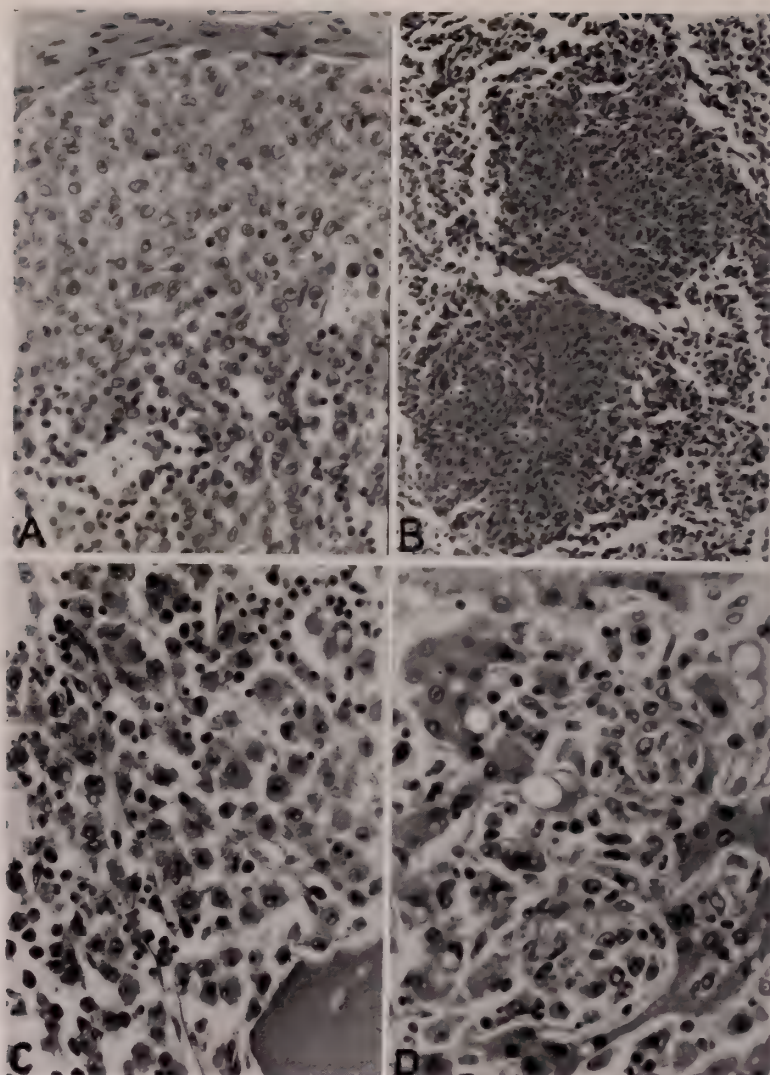


FIG. 3. Characteristic microscopic picture of Letterer-Siwe disease. Histiocytic cell proliferation of lymph node (A.), in bone marrow (C). Marked Kupffer cell proliferation of liver (D). Necrotic areas of lymph node (B).

loendotheliosis, because the latter terminology does not describe an acute virulent clinical course.

Some of the cases recently reported by Batson *et al* (11), differed from the case originally described by Letterer, it is doubtful that all their cases were Letterer-Siwe disease.

If one closely examines Carrington and Davison's well illustrated paper, in which the multiple abscesses in various bones proved to be due to *B. paratyphoid B*, one cannot help but interpret some of Batson's cases as simple multiple

bone abscesses, and not Letterer-Siwe disease. So too perhaps, were some of Green and Farber's cases (10).

SCHÜLLER-CHRISTIAN DISEASE

Schüller-Christian disease is an insidious, but steadily progressing systemic disease process, involving bones as well as visceral organs simultaneously. Characteristically, it is an extremely chronic process and takes a most protracted course.

When the so-called triad of exophthalmus, diabetes insipidus and defects of bones becomes apparent, the disease process is far advanced, and its onset, therefore, cannot be detected. For this reason, the exact duration of the disease in most cases is not known except in cases of young children.

However, there are reasons to believe that the disease process may exist for more than ten years, even 15 years, if vital organs, such as lungs are not extensively involved in the early stage of disease. When no diabetes insipidus exists, no early clinical diagnosis can be made. It is the diabetes insipidus which leads to the discovery of this disease. The lymph nodes enlargement or bone defects may sometimes lead to the diagnosis of this disease also.

According to Bennett (12), the complete clinical picture described by Schüller and Christian is dependent upon the proper localization of the underlying xanthomatous lesion. Therefore, this disorder should be designated a syndrome, and not a disease.

As this statement suggests, the clinical picture of this malady is very complicated. Nevertheless, it should be designated as a distinct disease, in my opinion, for the following reasons: It is well known that the initial location involved by a Hodgkin's disease granuloma varies greatly, in some cases it involves only abdominal lymph nodes. This may cause a variety of clinical pictures. I believe that the clinical picture of Hodgkin's granuloma 50 years ago would have been a most complex one. Yet, today one can recognize them as Hodgkin's disease, and not a syndrome, because the disease process has a definite pattern to diagnose it as a Hodgkin's granuloma. We, therefore, simply recognize a variety of this disorder.

Schüller-Christian disease is so rare that pathologists who have had more than 25 years' experience have not observed many more than a few. Not only is this malady extremely rare, but it occurs in a variety of types. For example, one case may begin with an extensive neck lymph node enlargement, without a sign of diabetes insipidus or bone defects. On the other hand, it may begin with bone defects. This has created much difficulty in understanding the true picture of Schüller-Christian disease. A clear-cut definition of this disorder is not easily obtainable. It was for this reason that Henshen (13) attempted to divide these conditions into eight groups.

Regardless of how the disease process may begin, when it is advanced, the lesion will form a granuloma that contains much cholesterol in foam cell form.

From the four cases of Schüller-Christian disease which I personally have

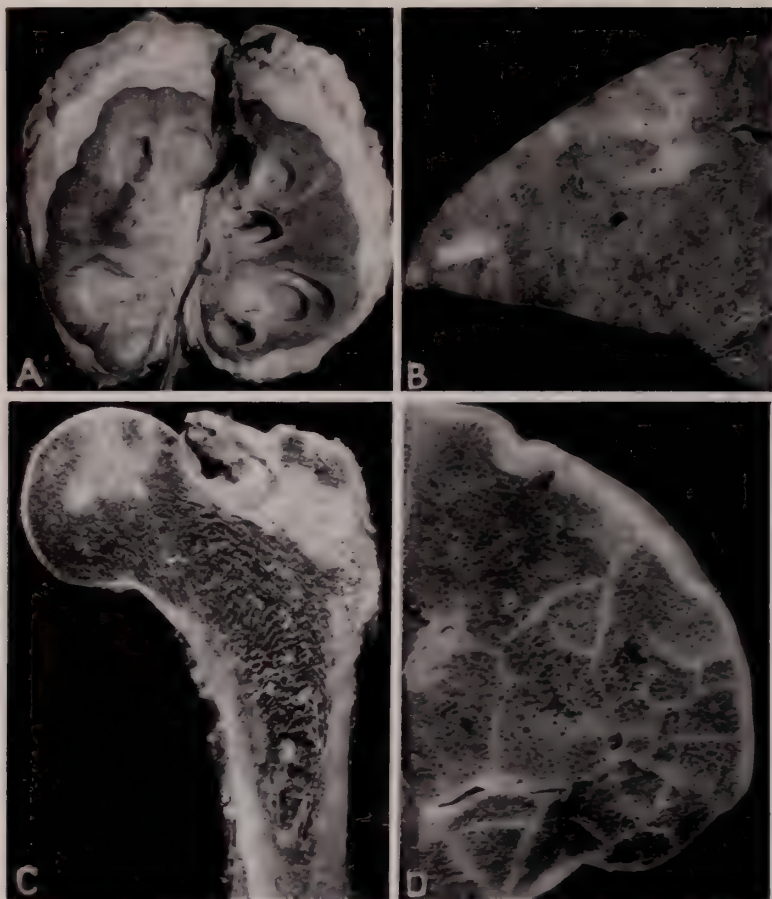


FIG. 4. Typical macroscopic picture of an advanced Schüller-Christian disease. Marked lipoid granulomatous lesions around the kidney (A), in the periportal areas of liver (B), Femur (C) and Lung (D).

observed, and from the literature, I shall present a composite picture, to illustrate this disease process.

I am of the opinion that this disorder is actually a granuloma-forming process, as in Hodgkin's disease, and that the fibrosing process is not a simple repair phenomenon of a previously necrotic lesion. To this granuloma, deposition of cholesterol appears in the form of foam cell. Just as in Hodgkin's disorder, this disease is a progressive one and it spreads to various organs and osseous tissue.

1. One of the most typical cases I observed showed very extensive involvement of many visceral organs. Lipoid granulomatous lesions were found in various portions of bones, lungs, liver, pancreas, testes, kidneys, heart and various parts of fat tissue (Fig. 4). The tumor-like granulomatous tissue with a large number of foam cells is a most characteristic feature of this condition.

It is noteworthy to describe organs of so-called reticuloendothelial system, such as Kupffer cells of liver, spleen or lymph nodes as not being involved. (This differs from those of typical Letterer-Siwe disease). The bones were involved,

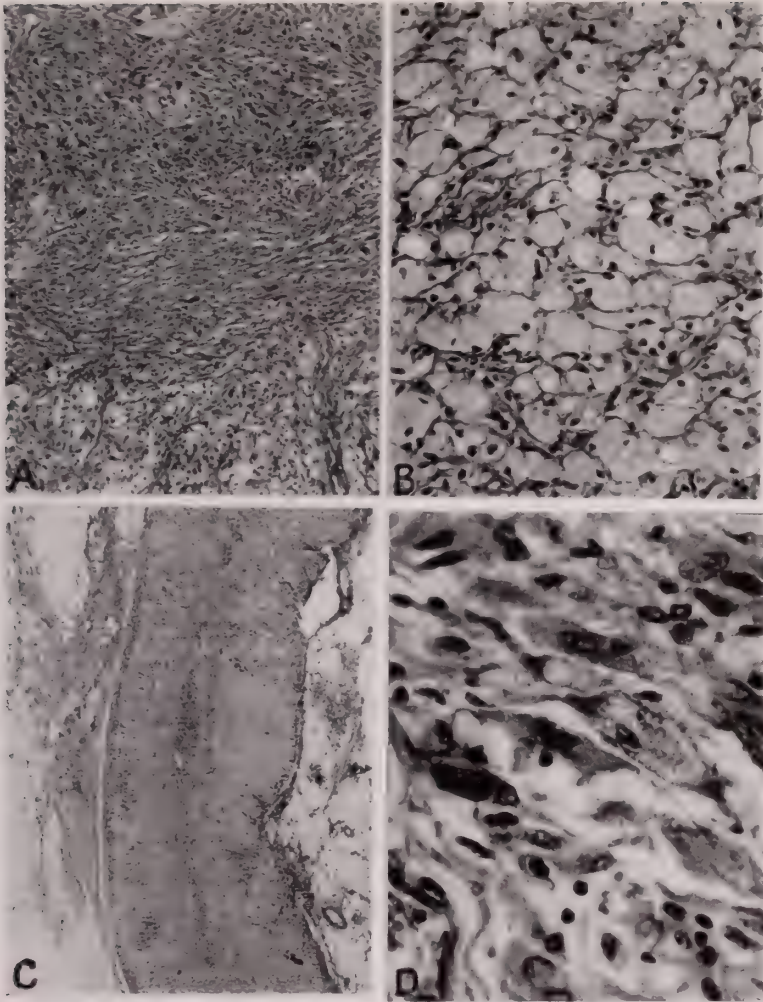


FIG. 5. Typical microscopic picture of Schüller-Christian disease. Lipoid granulomatous lesion (A). Accumulation of foam cells (B). Early granulomatous lesion of periadrenal fat tissue (C). (D) showing high power picture of (C). Note proliferating fibroblasts absorbing cholesterol; early foam cell formation.

but they were scattered and focal, and were not diffuse as in Letterer-Siwe disease.

As illustrated in Figures 5C and 5D, although this particular case was far advanced, an early lipoid granuloma formation was in progress in certain areas. Yet, lymph nodes were not involved. Extensive search revealed only a few foam cells in few lymph nodes.

2. Because of diabetes insipidus and bone defects, Schüller-Christian disease was diagnosed at the age of 12, but the patient survived 12 years. When he died, the lesions showed a typical lipoid granuloma. One of the lesions is shown in Fig. 6. A. to illustrate the actual granulomatous appearance.

It is usually mentioned in the literature that Schüller-Christian disease is

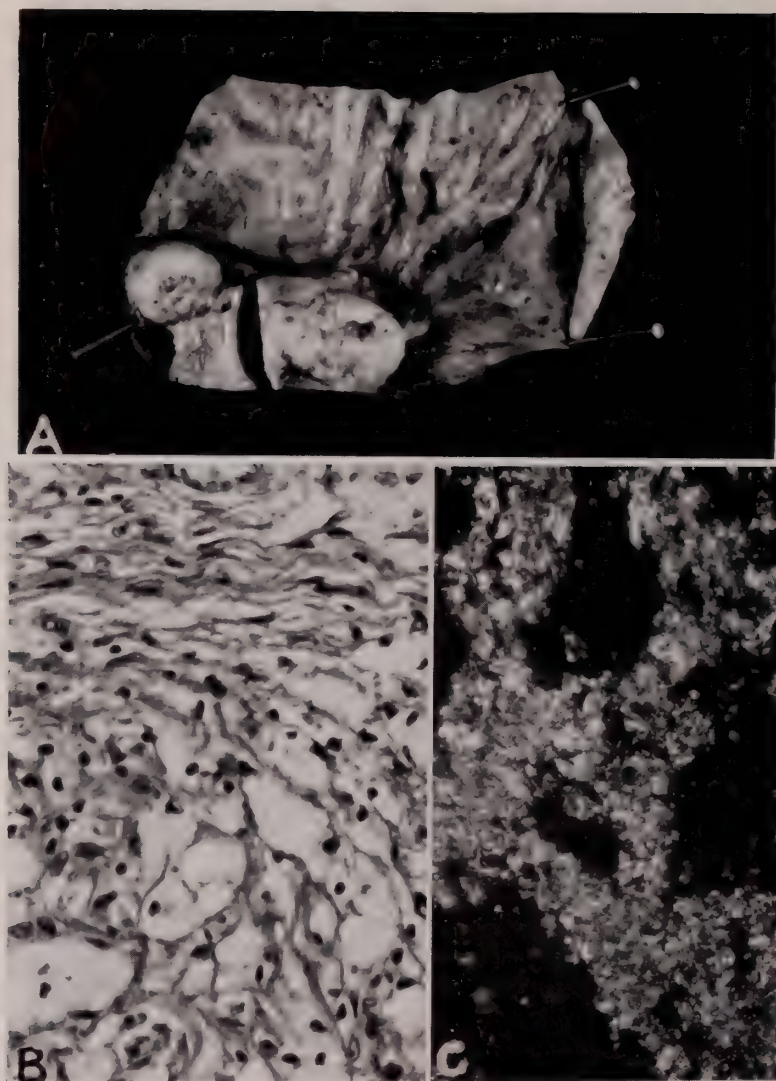


FIG. 6. Typical yellowish lipid granulomatous lesion of dura. Note tumor like mass formation (A). Its microscopic picture consisting of lipid granulomatous structure (B). Foam cell accumulation always showing doubly refractile cholesterol (C).

either reticuloendotheliosis or a bone disease. Many text books discuss this condition in sections devoted to bone pathology. It should, however, be considered as a systemic disorder as is Hodgkin's disease. It is improper to conclude that this disorder is either a bone disease or reticuloendotheliosis. This is borne out by the fact that the hepatosplenomegaly which is a constant finding in Letterer-Siwe disease has not been observed in the cases of Schüller-Christian disease.

In Letterer-Siwe disease, one finds proliferation of Kupffer cells in the liver,

while no such cell change is to be seen in Schüller-Christian disease. When the liver is involved in Schüller-Christian disease, it is the periportal spaces that show lipoid granulomatous changes.

Since there is no diffuse involvement of hematopoietic organs by lipoid granulomatous lesions in Schüller-Christian disease, it is impossible to term this condition a reticuloendotheliosis. The condition may be considered lipoid granulomatosis as an anatomical expression.

RELATIONSHIP BETWEEN LETTERER-SIWE DISEASE AND SCHÜLLER-CHRISTIAN DISEASE

As previously described, these two conditions are basically different, clinically and anatomically. If one is thoroughly familiar with each disorder, it is impossible to consider them as one entity.

Those who maintain that the two disorders basically are one entity must have had a different definition of Letterer-Siwe disease on the first place.

It has been claimed that a "transitional form" between the two conditions exist, and therefore, they should be classified as one entity. Wallgren's cases repeatedly have been cited as a "transitional form".

Wallgren himself stated that the histological picture of Schüller-Christian disease may be similar to that of Letterer-Siwe disease, and further stated that Letterer-Siwe disease is always fatal, whereas it is estimated that 30 per cent of the Schüller-Christian disease recover. This is an amazing statement that cannot be fully understood by pathologists who are familiar with the two disorders. One gets the impression that Wallgren might have been unfamiliar with those two conditions, or he must have had a completely different definition of these diseases.

His unusual two cases were regarded as transitional by many investigators. However, neither case had high fever, although there were skin manifestations. His cases were far from being typical Letterer-Siwe disease, which were regarded by Letterer as a type of septic condition. I share the opinion with Siwe (2) that Wallgren's cases should not be interpreted as "transition".

It is hard to understand Wallgren's statement that 30 per cent of Schüller-Christian disease recover, because Schüller-Christian disease is known as a progressive disease process. Some of the cases reported as Schüller-Christian disease because of multiple bone lesions, may have been simple multiple bone abscesses, as Carrington and Davison's type, because the latter condition is known to recover.

The occurrence of histiocytic cells in these conditions has been considered by some as the basic reason to consider these two conditions as identical. Such logic cannot be used, since a collection of histiocytic cells in lymph nodes occurs in various conditions, such as infectious mononucleosis. It is not the cells, but the whole disease pattern which must be considered, if one is to speak about the genesis of two disease processes.

Letterer-Siwe disease is a septic condition and always fatal, while Schüller-Christian disease is slowly progressing granuloma forming disease, similar to that of Hodgkin's disease. If one understands this basic difference between the

two, there will be no room for further discussion. There is no evidence to support the concept that the two conditions may have identical pathogenesis.

RELATIONSHIP BETWEEN EOSINOPHILIC GRANULOMA OF BONE AND SCHÜLLER-CHRISTIAN DISEASE

Eosinophilic granuloma of bone is known as a localized disease process, and Schüller-Christian disease as a progressive granulomatous condition. In the former, a complete healing has been recognized by practically all investigators. Nevertheless, recent authors on this subject are inclined to accept that they are basically one entity. Two reasons may account for this claim: (a) They interpreted them as reticuloendotheliosis without ground or they pretend there are cases of transformation between two disorders.

The occurrence of histiocytic cells in both conditions does not establish reticuloendotheliosis, because eosinophilic granuloma of bone is a localized bone lesion, and not a generalized disease process. This is evidenced by the fact that the bone lesion heals spontaneously. One finds histiocytic cells in lymph nodes in the early stages of Schüller-Christian disease. In the advanced cases, however, one can no longer find histiocytic cells. It is difficult to see why these conditions should be classified as reticuloendotheliosis.

They claim that transformation between the two conditions has been observed. This claim, however, should be critically analyzed. Is there such a transformation in authentic instances?

It would be rude, if one says there might have been an error of biopsy diagnosis in the published cases. However, one occasionally does see errors in biopsy interpretation. For instance, one of the cases reported as eosinophilic granuloma of bone, is obviously Hodgkin's disease (15). This is the reason why this particular case of eosinophilic granuloma of bone, suddenly shows axillary and mediastinal lymph node involvement. This unfortunately is not a single instance.

A biopsy of a bone lesion in a child was diagnosed by many pathologists as an eosinophilic granuloma of bone. On review of the same biopsy, I interpreted this as a case of Schüller-Christian disease. More than one year later, the child was readmitted to the hospital. The general x-ray studies of bones were reported as Schüller-Christian disease, and so was the final autopsy report. Pathologists who originally diagnosed this case as eosinophilic granuloma of bone, surely would claim that this is one example of the transformation, from eosinophilic granuloma of bone to Schüller-Christian disease. As far as I am concerned, it had never been an eosinophilic granuloma of bone, and no such transformation took place. It is easy to see that an erroneous diagnosis of the original biopsy may lead to a completely erroneous conclusion.

In general, an occasional diagnostic error in biopsy specimens can not be avoided. I recently discovered one such error on a lymph node biopsy interpretation. A lymph node was originally diagnosed as representing Hodgkin's disease. A year later another lymph node was diagnosed as lymphosarcoma. Here, one has to admit an error in diagnosis, instead of claiming a transformation of Hodgkin's disease to lymphosarcoma.

If one is thoroughly familiar with the basic pattern of these two disorders, one has to say that there is no reason at all for any possible transformation from one form to another. There is reason to believe that those who claim that such transformation is possible, might have been in error in interpreting the original biopsy specimens.

RELATIONSHIP BETWEEN EOSINOPHILIC GRANULOMA OF BONE AND LETTERER-SIWE DISEASE

The facts that eosinophilic granuloma of bone may go on to complete healing, and Letterer-Siwe disease is always fatal, have been more or less accepted, even by those who believe the concept of one basic disorder.

The two diseases are basically quite different from each other, clinically and anatomically. As long as one adheres to the definition of Letterer-Siwe disease and the type originally described by Letterer, there is no resemblance between the two disorders. There is no need for any further discussion to refute the claim that the two conditions are basically identical.

We have discussed the clinical and anatomical features which enable us to differentiate these three diseases. The differentiation on these grounds is particularly important, as the etiological factor as is yet unknown.

If one adds atypical cases and a general term such as histiocytosis X, to these well defined entities, he is obscuring the basic problem, and as such is offering little advancement in knowledge.

During the studies of various diseases, one always sees atypical cases. For example, the occurrence of so-called atypical Hodgkin's disease is well known. If one forcefully classifies it as Hodgkin's disease, the latter disease suddenly becomes a vague disease complex. One must, therefore, be extremely cautious not to mix atypical cases with already established diseases.

On looking over the many papers on eosinophilic granuloma of bone, Letterer-Siwe disease and Schüller-Christian disease, the inclusion of atypical cases is most likely responsible for the faulty conclusions.

To clarify this confusion is not only of academic interest, but it perhaps is important from a practical point. There is no reason at all to give a fearful prognosis when one faces a case of benign curable eosinophilic granuloma of bone. If one believes that Letterer-Siwe disease is of an infectious nature, then clinicians may concentrate their efforts to combat it with many therapeutic measures in an attempt to cure this hopeless condition. It is a pathologist's responsibility to clarify the issue.

SUMMARY AND CONCLUSIONS

1. Eosinophilic granuloma of bone is a fairly acute localized, destructive lesion of bone, and should be interpreted as osteomyelitis or bone abscess with a particular histiocytic and eosinophilic cell response. The lesion heals spontaneously. There is no reason to classify this condition as reticuloendotheliosis.

2. Letterer-Siwe disease is an acute, systemic, extremely toxic febrile disease

with generalized histiocytic cell response, and it is always fatal. The general picture resembles that of acute sepsis, as originally interpreted by Letterer. Anatomically it can be classified as infectious reticuloendotheliosis.

3. Schüller-Christian disease is a chronic lipid granuloma-forming disease process, and characteristically is a slow but definitely progressive disease involving various visceral organs as well as bones. Therefore, it should be classified as a systemic disease, and not a bone disease. Anatomically, it may be said to be lipid granulomatosis.

4. The clinical and pathological anatomical patterns of the three disorders differ so much, that there can be no resemblance among these three conditions.

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CORTISONE AND THE DISSOCIATION OF HYPERSENSITIVITY AND ACQUIRED RESISTANCE

EXPERIMENTS WITH HEAT-KILLED TUBERCLE BACILLI

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Although persistence of immunity in the absence of hypersensitivity has been demonstrated by desensitisation, the 'dissociation' of these two phenomena has not been accepted generally.

A further elucidation of the problem seemed possible by the use of cortisone. This represses the inflammatory response and also the resistance to multiplication and spread of such microorganisms as the tubercle bacillus. This would suggest that the depressant action on resistance was not coincident, but the result of diminished inflammatory reaction.

In the light of the experiments here reported this conclusion is open to doubt—at all events as far as acquired resistance to tuberculosis is concerned. In this respect, the experiments of Houghton and Davis (1) should be recalled, who failed to find any interference by cortisone treatment with the protection afforded by BCG vaccination.

In the present experiments the fate of heat-killed tubercle bacilli injected intradermally in sensitised guinea-pigs was studied. It had been shown previously (2) that heat-killed tubercle bacilli are rapidly disposed of at the site of intradermal re-injection. Would cortisone treatment interfere with this bacillary disposal, and if so, could such a reduction in local resistance be due to a depression of the hypersensitive tissue reaction?

The experiments here reported show that the disposal of heat-killed tubercle bacilli was at certain stages in no way affected by cortisone, in spite of a definite depression and retardation of the hypersensitive cellular response.

A rapid clearing of the tubercle bacilli—the corpuscular antigen—was demonstrable in tissue which, following cortisone treatment, showed the pattern of response of non-sensitised tissue. This suggested that the parallelism of reduction of hypersensitive tissue response and bacterial disposal seen at some stages is fortuitous and hence dissociable.

MATERIAL AND METHODS

Nine guinea-pigs were used. Four of these acted as controls, the five others received cortisone subcutaneously (either 2.5 mg. daily up to a period of six months or a single 'shock' dose of 50 mg. shortly before intradermal injection

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with heat-killed tubercle bacilli). The animals were sensitised by intradermal injection of 0.2 ml. of a suspension of heat-killed tubercle bacilli (H37RV strain) at an opacity equivalent to $1,000 \times 10^6$ B. coli per ml. into three separate sites. The papules which developed were observed daily.

Challenge injections of 0.2 ml. of heat-killed tubercle bacillary suspension were given into three abdominal sites 42, 120 and 207 days after the first injection. These will be called the 1st, 2nd and 3rd challenges.

The papules developing after each challenge were removed at varying intervals from two to 50 days after the sensitising and challenging doses (3).

Fourth Challenge

A 4th challenge injection was given one year and five months after sensitisation. Five animals were used, employing the methods of the previous experiments. Papules were removed on the 5th, 12th, 19th and 27th days after injection of tubercle bacilli. The animals used were Nos. 1, 9 (non-cortisone) and Nos. 5, 6 and 8 (cortisone).

RESULTS

I. Normergic Response

Injection of a suspension of heat-killed tubercle bacilli into the normal guinea-pig's skin elicits an abscess which is at its height after six days and disappears after the 16th day. Meanwhile a granuloma has developed. It consists of large macrophages and many giant cells of the Langhans type, which are full of acid-fast rods (Fig. 1). Between the 30th and 49th days there is a steady diminution of giant cells in favour of epithelioid cells, small macrophages and fibroblasts (Fig. 2). At the same time the number of acid-fast rods is perceptibly reduced, leaving a fine acid-fast intracellular 'dust' at the 49 day stage.

II. Response to First Challenge Without Cortisone

Already on the 6th day the abscess is minute and a granuloma is the predominating change (Fig. 3). Giant cells are sparse and no acid-fast elements are recognisable. *Sensitisation has caused the response on the 6th day to equal that reached by the normergic animal by the 49th day.* On the 30th day a small fibrous nodule remains in the sensitised animal in contrast to an extensive cellular granuloma with still considerable numbers of intracellular acid-fast rods in the normergic animal.

III. Response to First Challenge with Cortisone

On the 6th day there is a marked slowing down of the response compared with that in the untreated animals. The latter have already reached the stage of granuloma and complete disposal of the tubercle bacilli. In the cortisone-treated animals a granuloma has also formed, but the large initial abscess is still present, in which the disposal of the bacilli is not as complete as it is in the untreated sensitised animals; yet it is far more advanced than in the normergic animals. In fact, the sensitised, cortisone-treated animals have on the 6th day achieved a bacillary disposal comparable with that reached by the normergic animals

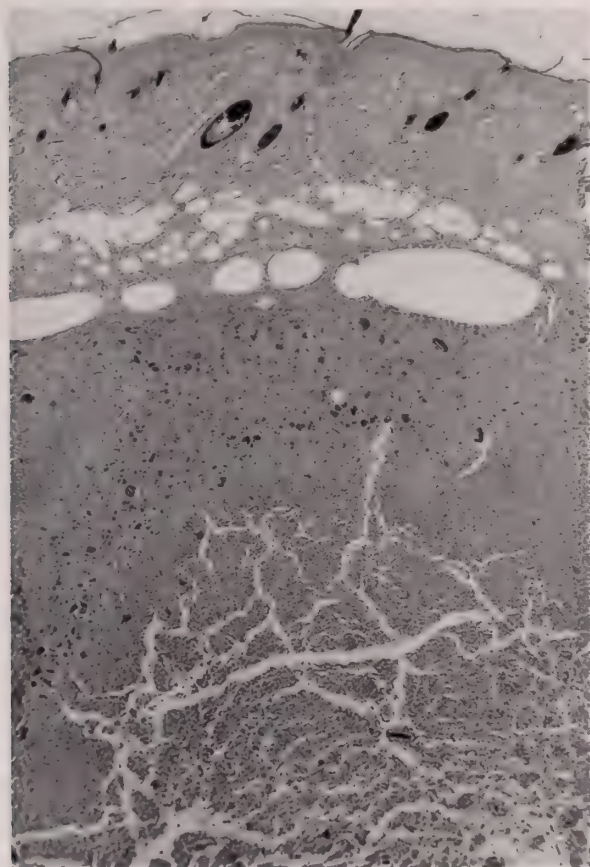


FIG. 1. Normergic response, 12 days. An abscess surrounded by granuloma, the latter containing many clumps of acid-fast bacilli (black). Ziehl Neelsen $\times 55$.

between the 30th and 50th days. It should also be mentioned that the site of the bacillary disposal in these animals is the *abscess* and not a granuloma, as is normally associated with the disposal of acid-fast bacilli, alive or dead.

In this respect the response on the 13th day is particularly instructive. *At this stage a clear dissociation can be demonstrated between the bacillary disposal and the tissue reaction normally credited with it.* Cortisone treatment at this stage has clearly interfered with the tissue response, but not with the bacillary disposal; the abscess has persisted but the bacilli have completely disappeared from it (Fig. 4). Cortisone preserved the normergic type of tissue response, but failed to interfere with bacillary disposal, for it has occurred inside a pure abscess and without the cooperation of cells such as macrophages, epithelioid and giant cells. In other words, *bacillary disposal was independent of cellular changes.*

IV. Response to Second and Third Challenges

Similar but less marked differences were observed after the second and third challenges. Owing to the long interval between sensitisation and challenge (120 days and 207 days respectively) there was no hypersensitive acceleration of

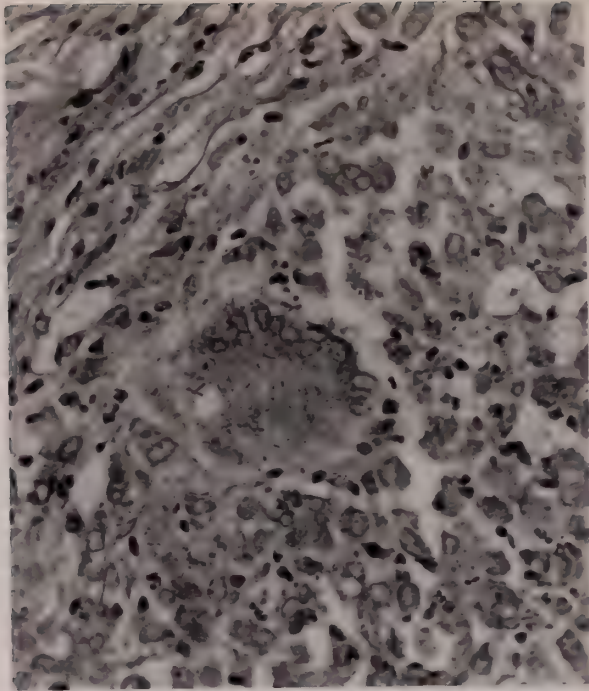


FIG. 2. Normergic response, 30 days. A giant cell surrounded by macrophages; both contain a diminished number of acid-fast bacilli, which are often granular. Ziehl Neelsen $\times 540$.

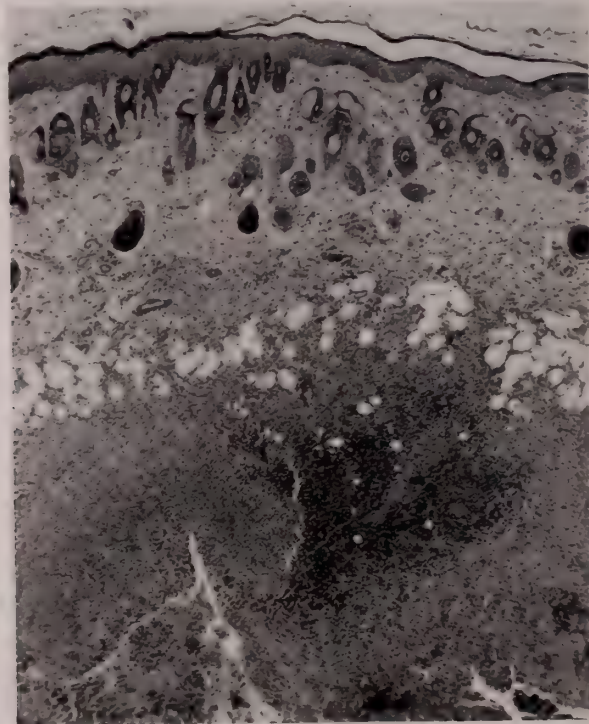


FIG. 3. First challenge, without cortisone, 6 days. Granuloma predominates, with a small central abscess. Haematoxylin & eosin $\times 55$.

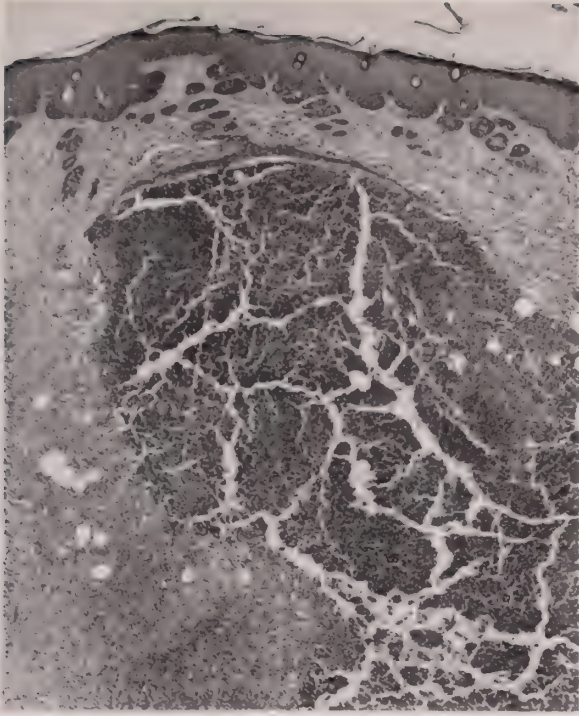


FIG. 4A

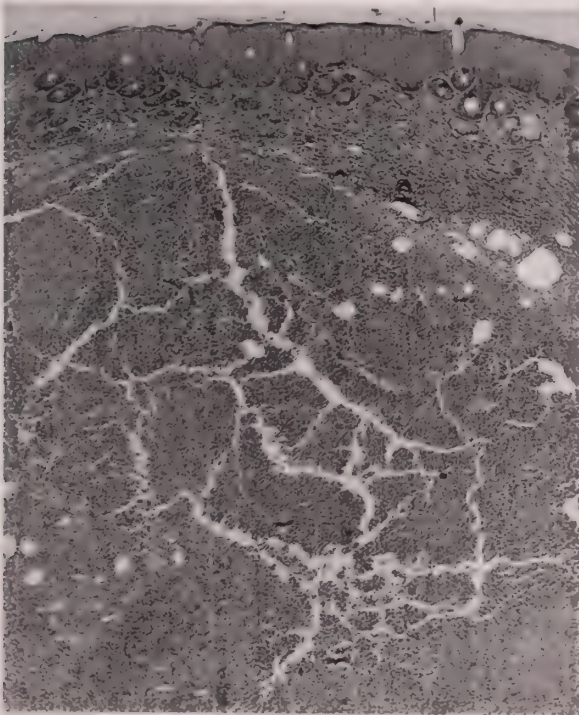


FIG. 4B

FIG. 4. First challenge, with cortisone, 13 days. (A) A large abscess persists with some surrounding granuloma (B). No acid-fast clumps are present (the black lines are artefacts). Ziehl Neelsen $\times 55$.

tissue reaction even in the non cortisone treated animal. Yet, there was a remarkable bacillary cleansing at the site of reinjection: bacillary disposal had taken place in a pure abscess without the action of macrophages, epithelioid and giant cells normally associated with it (3).

Here we have again a dissociation of resistance (as expressed by bacillary disposal) and hypersensitive inflammatory response.

V. Response to Fourth Challenge

Owing to the long interval between sensitisation and this challenge the hypersensitive response was perceptibly diminished and retarded. In the non-cortisone animals the granuloma was a little more conspicuous than the abscess up to the 19th day. The reverse was largely the case in the cortisone-treated animals. Bacillary disposal, however, was not related to these histological differences, large numbers persisting in both groups.

Clear-cut histological differences were recognisable only on the 27th day. In the non-cortisone animal cavitation and calcification were present, whereas in the cortisone-treated group a large granuloma and abscess were seen. Despite these histological differences there was *no* difference in bacillary disposal. In both groups acid-fast bacilli were by this time present in very small traces only.

COMMENT

The experiments reported provide a suitable model for the study of the disposal of corpuscular antigens in sensitised tissue under cortisone treatment. This treatment slowed the hypersensitive response down, following the well known pattern of the effect of cortisone on the tuberculin reaction (4, 5).

The depressant effect of cortisone on the hypersensitive tissue interfered to no comparable extent with the disposal of bacilli. Though setting in a little later than in the non-cortisone treated animal, bacillary disposal was still dramatic in the treated animal. Moreover, it occurred inside the initial abscess—neither special phagocytes, nor a granuloma, nor tuberculoid cells were required for the disposal of the heat-killed tubercle bacilli. Cortisone treatment thus affords another example of the 'dissociation' of the hypersensitive response and immunity. The latter—as shown by the speedy disposal of the antigen—takes place before and independent of the hypersensitive tissue changes.

It should also be noted that even after a lapse of 17 months some dissociation of response persists, in that a similar bacillary disposal occurs despite differences in histological pattern between those animals receiving cortisone and those that are not.

SUMMARY

Cortisone slowed down the hypersensitive histological response, but did not interfere appreciably with the disposal of heat-killed tubercle bacilli injected intradermally in the guinea-pig—despite the persistence of the initial abscess and retardation of the subsequent granuloma, the tubercle bacilli disappeared almost as quickly as in the untreated sensitised control.

The results presented provide further evidence that the cellular response is not an essential factor in the allergic disposal of corpuscular antigens.

ACKNOWLEDGMENT

The authors are indebted to Dr. Eugen Nassau for preparation of the bacillary suspensions and to Mr. J. E. Mayhew for technical assistance.

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AN ANALYTICAL SCHEMA FOR THE PATHOGENESIS OF PEPTIC ULCER: A FIRST APPROXIMATION

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An explanation of the nature of chronic peptic ulcer requires a framework in which anatomical, biochemical, physiological and clinical observations are correlated into a logical entity. At the present time the data available do not permit completion of such a framework. However, for heuristic purposes, and as a first approximation to such a goal it may be permissible to consider the problem in segments which are more easily handled. We have arbitrarily chosen to divide the problem into a consideration of (a), initiating factors, (b), perpetuating factors and (c), recidiving factors. This division was motivated by the realization that our own experimental studies were really concerned with only one facet of the complex problem with which the clinician deals in all its manifestations. It is not our purpose, however, to mold the blurred boundaries of the natural course of the disease into sharp, inflexible categories. We propose to use the above concept as a framework to orient our studies of the pathogenesis of chronic peptic ulcer.

Chronic peptic ulcer is a disease which is peculiar to man and any understanding of the disease will of necessity require a final analysis in relation to its subject. Analytic experiments performed on other species can therefore serve only as models or sources of analogy with all the limitations inherent in such data.

In our earliest studies we investigated the pathogenesis of acute, focal, ulcerative gastrointestinal lesions observed in a wide variety of clinical situations (1, 2). We concluded, as a result of clinical and anatomical correlations, that the occurrence of the lesions was associated with the evocation of the homeostatic phenomena usually occurring under stress, during the clinical courses presented by the patients. These observations were made in pre-antibiotic days and we still feel that the original correlation is valid despite recent reports of similar lesions following the use of a variety of antibiotics (3).

These acute ulcers are of interest for several reasons. We assumed that they were the result of the vasoconstriction which is part of the vasomotor homeostasis occurring under stress. If this were so, it should be possible to reproduce them by inducing a vasoconstriction, sufficiently severe and prolonged, to be comparable to that occurring in the clinical situation. We succeeded in doing this with the use of long-acting adrenalin and were able to produce similar acute erosions and ulcers in a variety of animal species (4). We realize that these experiments represent analogues. However, we were able to cause some of the

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ulcers to become "chronic" by this method. There is, furthermore, a small group of cases in which such lesions were observed in man in an acute phase and then were observed to become recurrent and chronic. These observations have been made in the case of Curling Ulcers following burns in young children in which the lesions bled, were demonstrated radiographically and were followed and observed to recur with the clinical picture of duodenal ulcer (5, 6). As a rule the earliest stages of development of chronic peptic ulcer are clinically obscure from the standpoint of etiology and pathogenesis. In this last group, however, we feel that clinical observations support the experimental analysis of initiating factors.

It is important to consider these initiating factors in a separate category in order to avoid confusion. Efforts are being made repeatedly to demonstrate the importance of the "alarm reaction" in the pathogenesis of chronic peptic ulcer (7). Such studies are usually made by attempting the demonstration of increase in steroid excretion in patients with chronic peptic ulcer (8). Such studies have almost always given negative results since they were done during the phase of reactivation or chronicity when the mechanisms which were active were those which did not elicit such changes. It must be only rarely that we would have an opportunity to study the systemic homeostatic mechanisms in this disease clinically. Even then the situations are so unusual as to characterize only an extremely small percentage of the total group of ulcer patients. As a result we are forced to rely on analogue or model experimental studies for the analysis of some possible initiating mechanisms involved.

Most studies of chronic peptic ulcer have concerned themselves with the mechanisms involved in the perpetuation and reactivation of the lesion without systematically differentiating these stages from each other, or from the initiating mechanisms. As a rule such investigations have implied the causative importance of the factors involved. We are loathe to discuss the "cause" of chronic peptic ulcer since we feel that the concept of cause applied to this disease pattern eventually leads into an unproductive, blind alley and to confusion. We believe, therefore, it is most important to study the mechanisms involved in the various stages of the disease as mentioned above, fully aware of the fact that these three factors may be produced in many ways and thus imply a spectrum of unrelated "causes".

Both experimentally and clinically the natural tendency of ulcers located in the stomach and duodenum is to heal. In most experimental studies in which surgical defects have been made in the mucosa, these have healed without any significant or obvious residual abnormality (9). It is an impression, unproved at this time, that this sequence of events must be a very common occurrence in man as well. Certainly the incidence of chronic peptic ulcer following acute Curling Ulcer is small.

What then leads to perpetuation of the lesion in some individuals? Systematic studies of this stage of ulcer disease are not available and we are compelled to invoke the factors of acid and pepsin as among the inhibitors of the healing process and among the more important perpetuating factors. Both of these have usually been considered as "causes" of chronic peptic ulcer. Since ulcers tend to

heal even when acid and pepsin are present in high concentrations it is difficult for us to visualize their importance as initiating factors. Obviously a wide variety of chemical and physical ingesta could be added to this list.

In contrast to the initiating mechanisms, the above perpetuating factors are locally produced and active. It follows that we conceive chronic peptic ulcer as a disease systemically induced but mainly locally perpetuated. We are led to this approach by the experimental observation that injurious substances, parenterally introduced, tend to elicit systemic, homeostatic activities which produce lesions which seem to localize in areas characteristic for the species studied. Thus dysentery toxin usually causes lesions in the gall bladder, duodenum and terminal ileum in the dog. It will be recalled that embryologically the gall bladder is a diverticulum of the duodenum. In the cat only minor lesions occur and these are in the stomach and colon; the same is true of the guinea pig. In the rabbit the lesion is almost entirely limited to the cecum (10). Such proximo-distal localization of these acute lesions, therefore, seems to have a genetic basis. That this is an important factor in human chronic peptic ulcer is becoming increasingly obvious.

We have recently become interested in another local factor which may play an important role in perpetuation and possible in reactivation of an ulcer. Aware of the occurrence of hypertrophied nerves in many chronic inflammatory lesions, we have been impressed with the frequency with which enlarged, almost neuromatous nerve endings are seen in the base of resected ulcers or in adjacent areas. These have usually been associated with sclerotic vessels. While we have not been able to differentiate afferent from efferent fibers in these lesions, it seems obvious that both must be present. Under these circumstances the exposed, neuromatous fibers act as sources of centripetal stimuli to the cord and thence to the central and peripheral nervous systems. Clinically this may be manifest in the occurrence of a zone of decreased temperature, which we have observed to be restricted to the skin area in which spontaneous ulcer pain is felt. This zone may persist for months after symptoms have cleared. We visualize this mechanism as the anatomico-physiological basis of Wernoe's symptom as well (11, 12). Of greater importance, however, is its possible effects as a source of stimuli which may on the one hand lead to a type of reverberating circuit (13) whose vasomotor component could prevent tissue healing and on the other, via ascending stimuli, perpetuate subjective symptoms even after the ulcer seems to be healed radiographically. This has obvious therapeutic implications.

The complexity of the chronic peptic ulcer problem is perhaps most manifest when we come to a consideration of the recidiving factors. Clinical observations have indicated a wide variety of such effective stimuli. On the basis of the heuristic paradigm which we have outlined these would include any or all of the systemic as well as the local factors which have been mentioned. Almost any factor capable of eliciting the systemic mechanism could serve as a recidiving factor. These could include the general responses to an external stimulus which might be purely psychologic, or the homeostatic reaction to an infection. The local injury resulting from ingesta have also been considered to play an impor-

tant role. This phase of the problem has been approached only on a gross clinical level and obviously forms an extremely complex and difficult subject for detailed analysis, certainly beyond the scope of this paper.

The opportunity to engage in these studies was made available through the continued efforts of Dr. Klemperer, over a period of almost two decades. His concept of "loyalty down as well as up" helped overcome many obstacles to its continuation, and served as a source of inspiration to further work. His stimulation and support of his subordinates, coupled with a sense of responsibility for their welfare and development was a source of the intense "esprit de corps" in his laboratory and of the continued devotion of those who proudly consider themselves his disciples.

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POTENTIATING ACTION OF SEROTONIN ON CHOLINE COMPOUNDS

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Recent studies by Woolley and Shaw (1, 2), and Marrazzi and Hart (3) have indicated that serotonin may influence various brain activities. According to Erspamer (4), and Page and coworkers (5), serotonin is widely distributed throughout the body; Page found the compound in relatively high concentrations in dogs', cats' and rabbits' brains as well as in muscle and nerve tissue. Therefore, according to Page "it may be an important link between muscle and nerve function." In addition, we have to mention the reports of Feldberg and coworkers (6-8) on the presence of choline compounds and related esterases in the mammalian central nervous system and their function as neurochemical mediators.

It is therefore, of interest to study the pharmacological relations between serotonin and choline compounds, particularly if a possibility exists that, serotonin and choline compounds, given together, have a strong *in vivo* influence.

Our experiments were carried out on the isolated guinea pig ileum, a very sensitive preparation for the examination of choline compounds, particularly acetylcholine chloride. This drug produces an immediate and strong contraction of the suspended ileum, when given in doses as low as 0.025 γ per 20 ml. Tyrode-solution. Furthermore, it is rapidly hydrolyzed by cholinesterase to choline and acetic acid. We also used more stable compounds, such as methacholine chloride (acetyl- β -methylcholine-chloride, mecholyl), which is less readily hydrolyzed by cholinesterase than acetylcholine. Another compound investigated was carbachol (choline chloride carbamate also known as Doryl, Lentin or Carcholin). This particular drug is very stable in the body and it is insusceptible to hydrolysis by cholinesterase, neither are its effects in any way prolonged or enhanced by physostigmin or neostigmin. Finally, we used bethanechol or Urecholine chloride, which is also stable and is not hydrolyzed by cholinesterase, being therefore, with a long duration of action in the body. The pharmacological properties of these related drugs have been extensively investigated by Molitor (9).

METHOD AND RESULTS

The effective doses of serotonin were found to be between 1.0 and 2.5 γ added to 20 ml. of Tyrode-solution, e.g., 0.05 γ -0.125 γ of serotonin per ml. of bath fluid. These very low serotonin concentrations usually take 10 to 20 minutes to influence the suspended ileum preparation, in which time the metabolism and the excitability of the smooth muscle may be changed. The response was first

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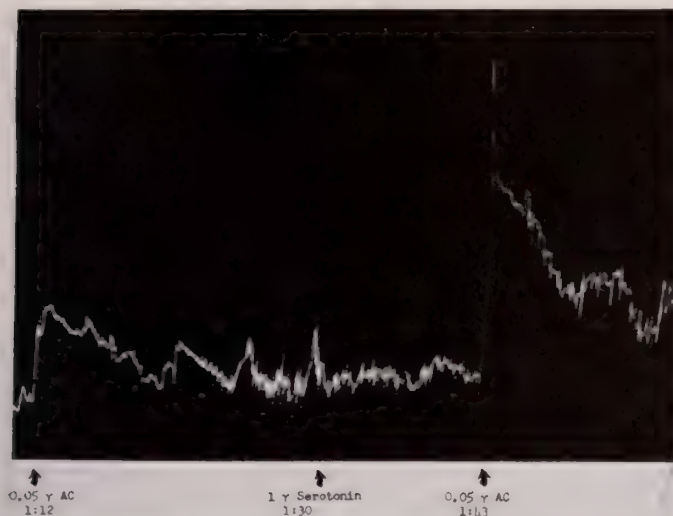


FIG. 1. The enhancement of the Action of Acetylcholine by Serotonin. Isolated guinea pig ileum in 20 ml. Tyrode solution.

established to small doses of acetylcholine, usually 0.05γ in 20 ml. Tyrode. The acetylcholine was washed out by changing the Tyrode solution in the baths, so that the contracted muscle returned to its normal state of relaxation and peristaltic motility. One of the above mentioned doses of serotonin was then added to the preparation and was left to remain there for 10 to 20 minutes. At the end of this period the response of the ileum strip was again established to the same dose of acetylcholine used at the beginning of the experiment. A comparison of the kymographic tracings of the length of the contractions of the strip before and after the addition of the small amounts of serotonin gives a good demonstration of changed responses of the isolated ileum muscle. The following experimental protocol gives a good example of such experiments (Figure 1).

I. Potentiating action of Serotonin on Acetylcholine Chloride

The response of the isolated ileum strip was first tested (at 1¹² hours) with 0.05γ acetylcholine chloride; this dose produced a small contraction of 3 cm. length. The drug was then washed out by changing the Tyrode solution. After a short period, 1.0γ of serotonin was added (at 1³⁰ hours). This induced a very small and short-lasting ileum contraction. The serotonin was left in the organ bath for 13 minutes without producing any motor alteration in the suspended ileum. At the end of this period (at 1⁴³ hours), the originally used small dose of 0.05γ of acetylcholine was again added. The strip responded with a potent contraction of 10 cm. length. A comparison of the response of the ileum to 0.05γ of acetylcholine before and after serotonin shows that the 13 minutes pretreatment of the strip with 1.0γ of serotonin produced more than a threefold increase in the length of the contraction.

II. Potentiating action of serotonin on Mecholyl, Doryl and Urecholine

The enhancement of action by serotonin of all these stable choline esters was examined. The effects of these drugs on the intestinal muscle were not as strong as those of acetyl choline; therefore, they were used in the higher doses of 0.1 to 2.0 γ . Because of the weaker effect of these drugs, a strong potentiation of action was not expected as in the case of acetylcholine. The kymographic records show the potentiation of all these stable choline esters by 1 γ to 2.5 γ of serotonin and prove that the enhancement of these stable choline esters may be independent of a cholinesterase inhibition. Several typical experiments are shown as examples (Figures 2, 3 and 4).

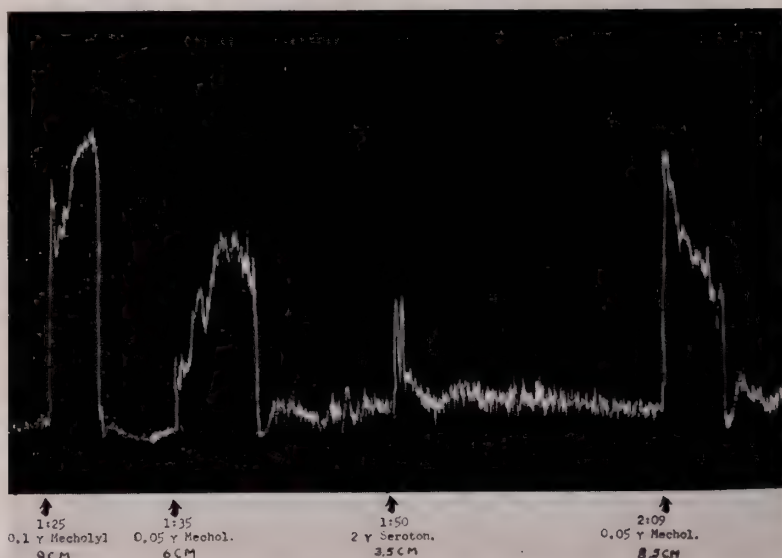


FIG. 2. Enhancement of the Action of Mecholyl by Serotonin. Isolated guinea pig ileum in 20 ml. Tyrode solution.

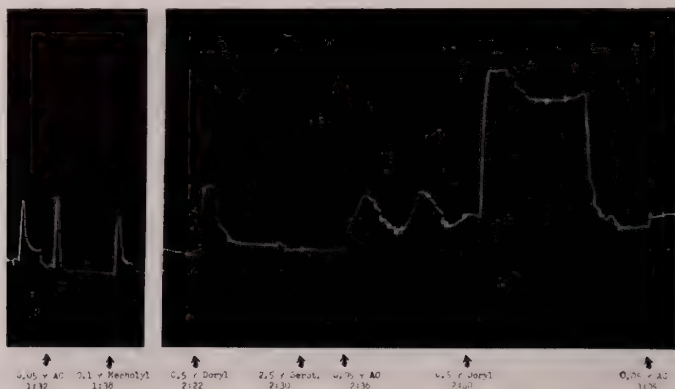


FIG. 3. Enhancement of the Action of Doryl by Serotonin. Isolated guinea pig ileum in 20 ml. Tyrode solution.

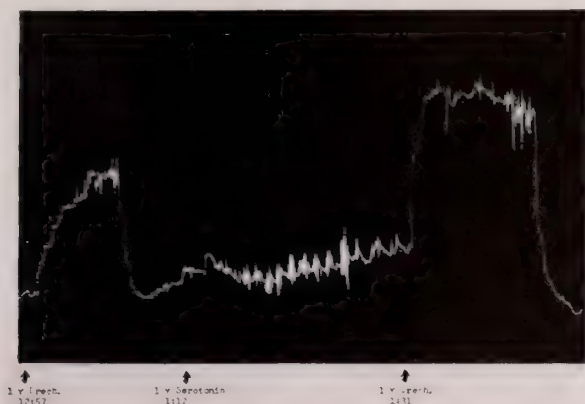


FIG. 4. Enhancement of the Action of Urecholine by Serotonin. Isolated guinea pig ileum in 20 ml. Tyrode solution.

a. *Enhancement of the action of 0.05γ Mecholyl by 19 minutes pre-treatment with 2γ of serotonin (Figure 2).*

1st Control (at 1²⁵ hrs.)

0.1γ Mecholyl:

length of contraction of untreated strip 9 cm. Change of Tyrode solution.

2γ serotonin (at 1⁵⁰ hrs.)

3.5 cm. contraction. No change of Tyrode solution.

2nd Control (at 1³⁵ hrs.)

0.05γ Mecholyl:

length of contraction of untreated strip 6 cm. Change of Tyrode solution.

0.05γ Mecholyl (at 2⁰³ hrs.)

length of contraction of serotonin pre-treated strip 8.5 cm.

The reaction of the sensitized ileum strip to 0.05γ mecholyl is therefore nearly as strong as the reaction to 0.1γ mecholyl of the nonsensitized strip and much stronger as compared to the response of the untreated strip to 0.05γ Mecholyl.

b. *Enhancement of the action of 0.5γ Doryl by 10 minutes pre-treatment with 2.5γ serotonin, (Figure 3).*

Control (at 2²² hrs.)

0.5γ Doryl length of contraction of untreated strip 2.7 cm. Change of Tyrode solution.

0.05γ Acetylcholine (at 2³⁶ hrs.)

length of contraction 2.5 cm.

2.5γ serotonin (at 2³⁰ hrs.)

no reaction. No change of Tyrode solution.

0.5γ Doryl (at 2⁴⁰ hrs.)

length of contraction of serotonin-treated strip 6 cm.

The reaction of the sensitized ileum strip to 0.5γ doryl was actually more than double in comparison to the response of the untreated strip to the same dose of Doryl.

c. *Enhancement of the action of 1 γ Urecholine by 19 minutes pre-treatment with 1 γ serotonin (Figure 4).*

Control (at 12 ⁴⁷ hrs.)	1 γ serotonin (at 1 ¹² hrs.)	1 γ Urecholine (at 1 ³¹ hrs.)
1 γ Urecholine length of contraction of the untreated strip 5 cm. Change of Tyrode solution.	length of strip contraction 1.5 cm. No change of Tyrode solution.	length of contraction of the serotonin - treated strip 6.5 cm.

The above examples clearly demonstrate, that the phenomenon of sensitization of the intestinal muscle strip can also be effectively produced with the stable choline esters without inhibiting effects on cholinesterase. Gaddum and Hameed (10) have demonstrated that the action of serotonin on the rabbit's ear was increased, when ephedrine or choline-paratolyl-ether bromide (1 mg./l) was present in the perfusion liquid; they believe that this potentiation of the vasoconstrictor effect of serotonin is due to the inhibition of amine-oxidase. This hypothesis may be very attractive in some cases but is not generally applicable. Since vitamin B₁₂ (cyanocobalamine) is also an excellent sensitizer (unpublished results, to be reported elsewhere), the following experiments were performed, in which the sensitizing action of drugs were compared.

III. *Cyanocobalamine (Vitamin B₁₂) and the Desensitization Action of Serotonin*

Both of these agents are important sensitizers of the normal action of the intestine; serotonin, however, according to Gaddum (10-11), Erspamer and others (4) is inhibited by various ergot alkaloids, as well as by lysergic acid diethylamide, Stoll (12). This latter drug, which inhibits adrenalin, also specifically inhibits the vasoconstrictor action of serotonin. It leaves unchanged, however, the action of carbacholyl on the rat's uterus (13-14).

In our studies, in agreement with Gaddum, we find that treatment with serotonin causes such a strong desensitization of the suspended guinea pig ileum that, even after relaxing for several minutes, the muscle will not respond to a repeated addition of serotonin, although the response to histamine according to Gaddum remains unchanged. The results from an experiment demonstrating the desensitization of an intestinal strip to repeated doses of serotonin are shown on Figure 5. Doses of 2.5 γ serotonin were administered at approximately 10 minute intervals. As can be seen from the figure, the third dose of serotonin (at 12:53 hrs.) produced a considerably weaker contraction of the strip as compared to the original response at 12:32 hrs.; the administration of a fourth dose (at 1:03 hrs.) failed to induce any contraction at all. The addition (at 1:08 hrs.) of 2.0 γ of cyanocobalamine, a strong non-specific potentiator, failed to antagonize the desensitization of the guinea pig ileum to a repeated dose of serotonin at 1:20 hrs.

A further example of the phenomenon of desensitization of the ileum to repeated doses of serotonin, and of the inability of cyanocobalamine to antagonize this phenomenon, is presented on Figure 6. Here, 1.0 γ doses of serotonin administered at 1:08, 1:25 and 1:57 hrs., produced progressively diminishing contractions of the strip which were not potentiated by the addition of 5.0 γ of cyanoco-

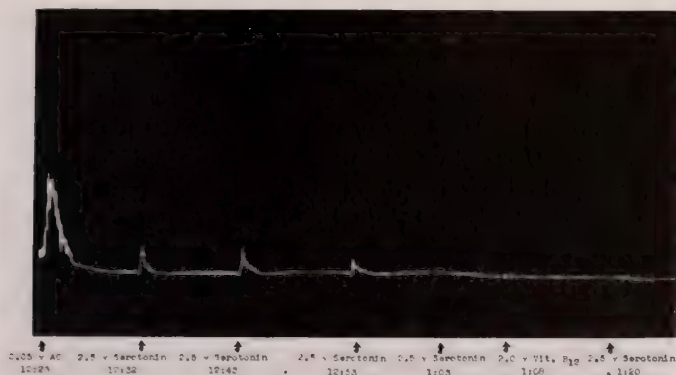


FIG. 5. Desensitization of the Intestinal Strip to Repeated Doses of Serotonin. Failure of Vitamin B₁₂ to antagonize this effect of serotonin.

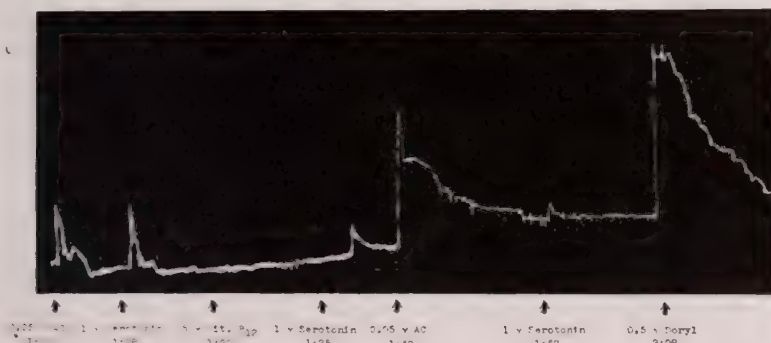


FIG. 6. Desensitization of the Intestinal Strip to Repeated Doses of Serotonin with Potentiation of the Action of Acetylcholine and Doryl.

balamine at 1:20 hrs. This figure also shows that, despite of the desensitization of the strip to serotonin, this drug continued to exert its potentiating effect on the response of the intestinal muscle to cholinergic drugs. A comparison of the contraction induced by 0.05 γ of acetyl choline at 1:00 hrs. with that observed with the same amount of acetylcholine at 1:40 hrs., clearly demonstrates the strong potentiating effect of 1.0 γ of serotonin, administered at 1:25 hrs. These results indicate that the phenomenon of desensitization of the intestinal strip may be specific for serotonin alone, and that it has no influence on the enhancement of other chemical reactions in the muscle metabolism.

SUMMARY

1. We have investigated the effect of serotonin on the response of isolated guinea pig ileum strips to acetylcholine. It was found that pretreatment, of 5 to 15 minutes duration, with small doses (1.0 to 2.0 γ) of serotonin strongly potentiated the effect of acetylcholine. This was determined by comparing the length of the acetylcholine-induced contractions of the strips before and after treatment with serotonin; in some cases more than a three-fold increase in length

of contraction was observed (Figure 1). These results clearly indicate a serotonin-induced sensitization of intestinal muscle to a cholinergic drug.

2. In order to find out whether this sensitization is dependent on the inhibition of cholinesterase several other choline compounds were investigated, such as: Mecholyl, Doryl and Urecholine. These drugs are stable choline-compounds; Mecholyl is less readily hydrolyzed by cholinesterase than acetylcholine, and the latter two are not hydrolyzed by cholinesterase at all. Our results have shown that small doses of serotonin enhance the response of the isolated guinea pig ileum to Mecholyl, Doryl and Urecholine (Figures 2, 3 and 4). Therefore, it seems that the enhancement of the action of cholinergic drugs by serotonin could not be explained on the basis of cholinesterase inhibition.

3. In agreement with Gaddum, we have demonstrated the phenomenon of *desensitization* of the intestinal muscle to repeated doses of serotonin (Figures 5 and 6). This desensitization to serotonin was found not to be antagonized by *cyanocobalamine*, which in other experiments was proven to be a *strong potentiator*. The observation that the desensitized-to-serotonin ileum strip still responds to cholinergic drugs with increased contractions, indicates that the phenomenon of desensitization is specific for serotonin alone (Figures 5 and 6).

CONCLUSION

Our experiments demonstrate for the first time the enhancement of the action of cholinergic drugs on cholinergic muscles and nerves by small (1γ to 2.5γ) amounts of serotonin. Such small amounts of serotonin may be present in various organs and tissues under normal or pathological conditions (3). The pharmacological studies of the enhancement of cholinergic agents appears to be important in the analysis of the serotonin action on the metabolism of brain and other organs.

ACKNOWLEDGEMENT

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THE NOTCHED NUCLEUS OF THE FAT CELL (UNNA'S "LOCHKERN")

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Morphology, normal and pathological, has been declared dead or dying many a time, but again and again it has put the prognosticators to shame. These recurrent revivals are not necessarily achieved by the use of modern tools like the electron microscope or the phase contrast outfit; some can be staged by loving attention to detail in the pathologist's daily work. One neglected, but by no means novel, histological detail, namely the notch in the nucleus of the fat cell, has lately aroused my curiosity.

Our modern idea of the connective tissue as an active and suffering component of the body has been shaped to a large extent by Paul Klemperer. He has helped to free it from the ignominious role of "supporting tissue". Thus it may not be amiss to have in his *Festschrift* a few remarks about the other tissue that recently has risen in the hierarchy of physiology and pathology, namely the fat tissue.

In 1895 the dermatologist, Unna (1), described "punched out holes" in the fat cell nuclei of the subcutaneous tissue and the bone marrow. Their diameter varied from an eighth to a half of that of the nucleus; sometimes they formed a groove. Unna (1) recommended their study to the professional histologists. He gave no illustrations. In the same year, Sack (2) wrote a paper on "vacuolized nuclei of the fat cells. . . ." that included beautiful illustrations (Fig. 1). He believed that the vacuoles, which he did not consider fatty, were formed in the nucleus and sometimes broke through outwards. One year later, the Viennese anatomist, Rabl (3), refuted Sack's conclusions (2). He showed that the seemingly intranuclear vacuoles were situated in a deep niche, actually outside the nucleus, and he proved their fatty nature by staining them with osmic acid.

Unna's recommendation to the histologists (1) was carried out only to a point. Stöhr's much used textbook of histology (4) mentions that the nucleus in fully developed fat cells regularly contains one or more sharply circumscribed small droplets of fat. Maximow (5), Schaffer (6), and Patzelt (7) also mention it. To enumerate the many pertinent books and papers from different countries that do not refer to this phenomenon would be wasteful and tedious. It is passed over in chapters that deal with the morphology of adipose tissue, even when the authors were especially interested in the problems of fat tissue. No photomicrographs are available in the literature, as far as I know, but there are some good drawings (Fig. 1). Krainer (8) in 1935 made use of the "Lochkern" for the identification of intracranial fat cells.

The diagrammatic sketch (Fig. 2) illustrates the different aspects under which the notch appears in sections and explains why it often cannot be seen at all. Its

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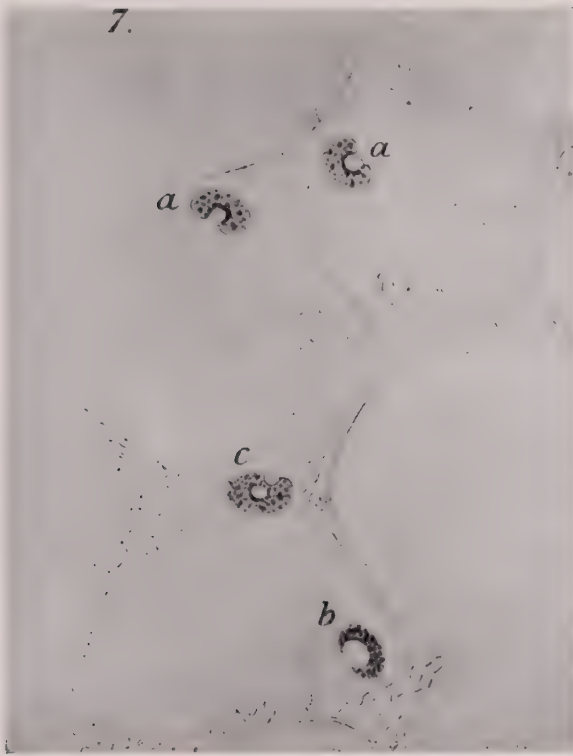


FIG. 1. From Arnold Sack, Ueber vacuolisierte Kerne der Fettzellen. Archiv f. Mikroskop. Anat. (1895) 46: 431, Fig. 7 on Tafel XXII. Four characteristic fat cell nuclei. The one indicated by the letter "c" shows two indenting droplets—the position of the larger one corresponding to the level E-F, in the diagram in Figure 2.

nature as it appears to me at present, namely that of a continuation of the large fat droplet, is not often seen (Figs. 3–6). In Figure 3, which is taken from fat tissue in a human parathyroid gland, two-fifths of the circumference of the nucleus is concave, giving it a canoe shape. The nucleus in the corner of the picture shows a smaller similar concavity or, perhaps, a marginal, edgewise cut of a large one. Only a small portion of the fat cell is visible in Figures 3 and 4, and this is often the case when the notch is seen as described. This indicates that certain orientations of the notch are more frequent than others. The droplet very seldom comes near the opposite surface of the nucleus (Fig. 5). Figures 3–6 correspond to levels illustrated in the left half of the sketch (Fig. 2). The usual aspect, corresponding to level E-F is shown in Figures 7–9. It led Unna (1) to adopt the name "Lochkern" (the nucleus with a hole) which might be changed to "Kerbenkern", the notched nucleus. One easily sees from the sketch that many sections will miss the notch (levels like C-D), and that others, A-B for example, may show a pinpoint hole. Rabl (3), while studying the seemingly intranuclear vacuoles in isolated fat cells, realized that there was only one position of the micrometer screw at which he could see chromatin structures in the area of the droplet. From that he justly concluded that the droplet cannot be truly intra-

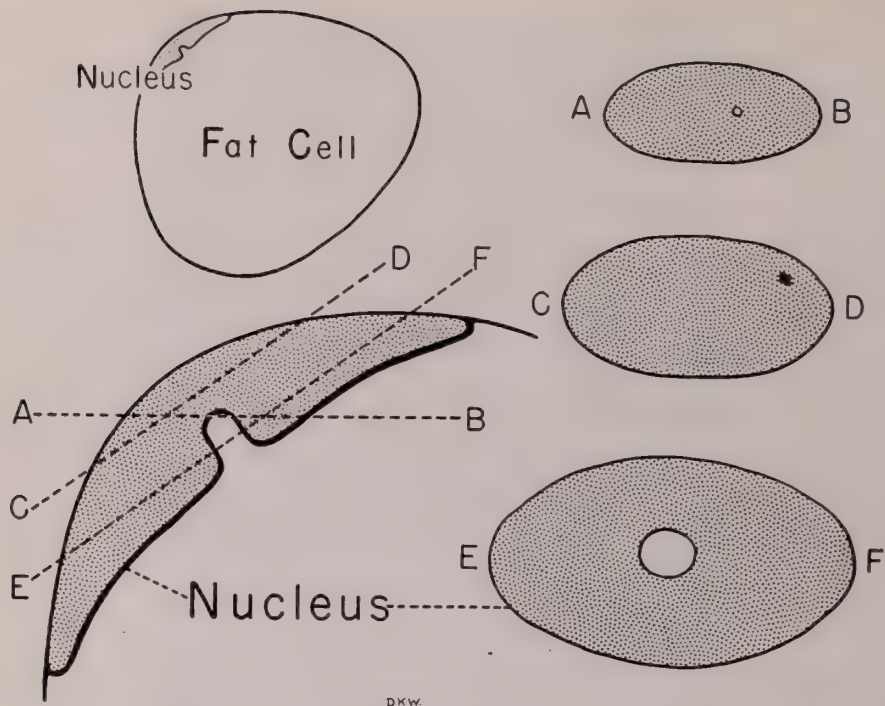


FIG. 2. Diagrammatic sketch of fat cell with notched nucleus (see text).



FIG. 3. From fat tissue in parathyroid gland. Two fat cell nuclei are in focus. The one in the center is indented by a large fat droplet, the one in the left lower corner by a small one. AFIP Acc. No. 721069, Photo. No. 55-20576, H&E 1260 X.

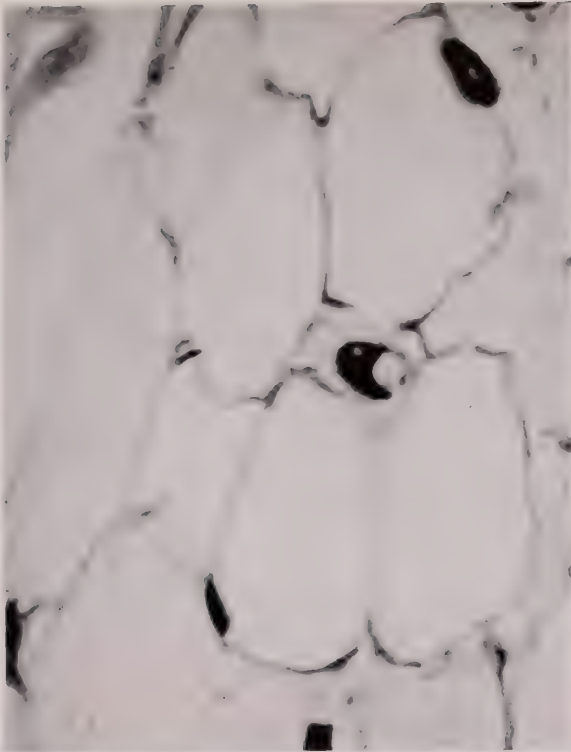


FIG. 4. From orbital fat tissue. The fat cell near the center has been cut almost tangentially at the level of the nucleus, and thus only a small segment of the fat cell is seen. (Compare with Fig. 3.) The seemingly intranuclear droplet has a faint outline towards the large droplet that fills the cell. AFIP Acc. No. 482185, Photo. No. 56-23875, H&E 1100X.



FIG. 5. From an adrenal myelolipoma. The nucleus of a somewhat distorted fat cell appears almost bisected by the unusually large indenting droplet. It is possible that the shape of the droplet also has been altered mechanically. AFIP Acc. No. 302500, Photo. No. 56-23862, H&E 1200 X.

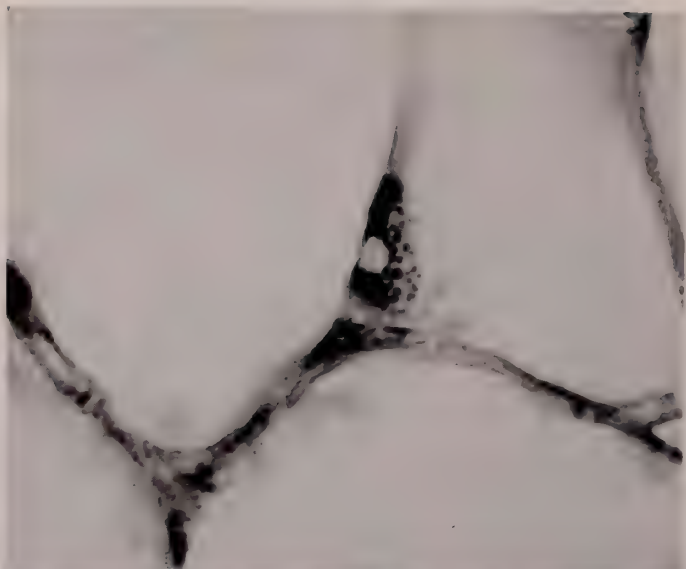


FIG. 6. From an adrenal myelolipoma. The cytoplasmic ring of the fat cell is seen through the area of the indenting droplet. This proves that the droplet is not intranuclear. (See text.) AFIP Acc. No. 547192, Photo. No. 56-23863, H&E 1200 X.



FIG. 7. From periadrenal fat tissue of an adult rabbit. This is the most frequent appearance of the notched nucleus. There seems to be a punched-out hole in the nucleus; hence Unna's original term "Lochkern". (Loch means hole.) Photo. No. 56-13587, H&E 1400 X.

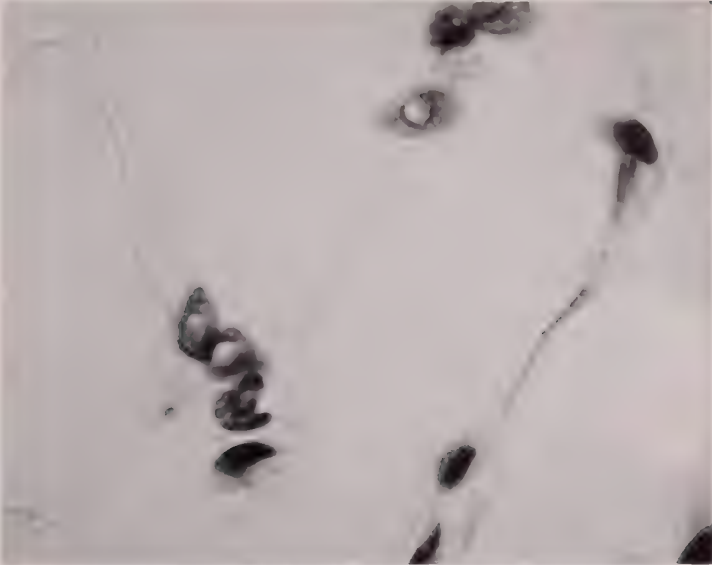


FIG. 8. From periadrenal fat tissue of an adult rabbit. Three characteristic fat cell nuclei, two of them near each other. Photo. No. 56-13586, H&E 950 \times .

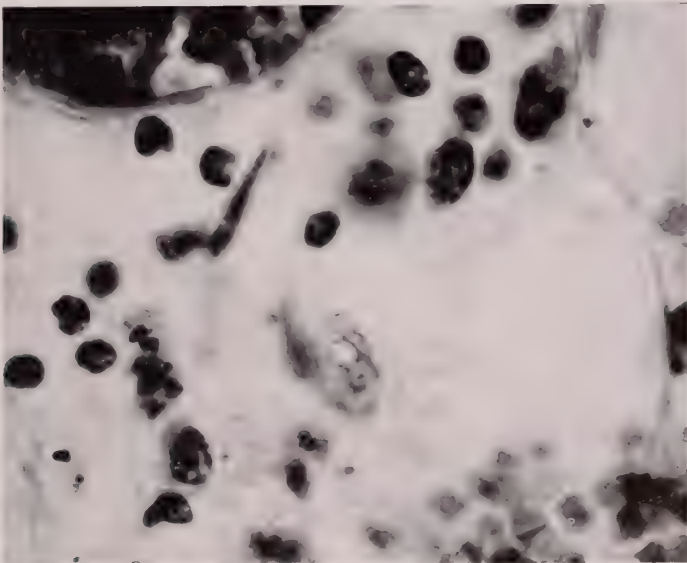


FIG. 9. Notched nucleus of a fat cell within the adrenal cortex. (The adrenal tissue cannot be recognized in this field.) The characteristic nucleus indicates that this is a genuine fat cell, not a transformed parenchymal cell of the adrenal cortex. AFIP Acc. No. 520518. Photo. No. 57-1295, H&E 1450 \times .

nuclear. A similar optical situation is represented in Figure 6 in which the cytoplasmic ring of the fat cell is seen through the area of the indenting droplet. This would be impossible if the droplet were surrounded on all sides by nuclear matter.

The literature states that the indentation disappears when the fat cell becomes atrophic. This was essentially but not entirely borne out by a study of 35 autopsies in which inanition or malnutrition was one of the main diagnoses. All bodies were those of adult males of average height, and most of them had an estimated weight of 95 pounds or less. The number of notched nuclei that could be found in the available routine paraffin sections generally was roughly proportional to the size of the fat cells, and the very small fat cells, which sometimes could barely be recognized as such, did not show the notch. But there were exceptions. In six cases the "holes" in the nucleus were found in spite of severe atrophy, while occasionally they were absent when atrophy was only moderate. The number of observations is small, and interpretation even of a large series would have to reckon with the following handicaps: A long search may be necessary before indented nuclei can be found in normal fat tissue; why, I do not know. Furthermore, single non-atrophic fat cells can be seen in otherwise severely atrophic fat tissue, and since it is by no means easy to decide in every case to which fat cell a nucleus belongs, the notched nucleus of a fairly normal fat cell might erroneously be ascribed to a neighboring atrophic one. A further difficulty in judging the size of a fat cell lies in the fact that the nucleus is best seen when the cell is not cut through its largest diameter but more tangentially.

Similar considerations apply to the fat tissue of the newborn. I studied material from nine mature newborns and two premature ones (47 cm., 40 cm.). Notched nuclei were found in seven, including the two premature ones. As in the cases of inanition, their number was generally, but not always, in ratio with the size of the cells. I have not yet studied the fat cell nuclei of younger fetuses.

Some fat cells, notably in areas of atrophy, show small or large, round but not sharply outlined, more or less clear spots which may create doubt as to whether they belong to an indenting droplet, at or near the level A-B (Fig. 10). On the whole, I think that they do not interfere seriously with the statements about the presence of notched nuclei.

Nobody seems to know whether or not every adult fat cell has a notched nucleus. Stöhr (4) called it a regular occurrence, while Unna (1), Schaffer (6), Maximow (5), Patzelt (7), and Wassermann (9) expressed the belief that it occurs often but not in every adult fat cell. Having worked with sections only, I am in no position to make a statement about this. As mentioned above, fat cells sectioned only at certain levels show the notch, and when the nucleus is large and the notch is small, it is missed at most levels. Obviously, it is impossible to learn from the study of single sections whether or not every fat cell nucleus is notched. Observation of isolated fat cells may solve the problem.

Tissues from the few mammals I could examine gave the same picture—fat cell nuclei are notched in the mouse as well as in the giraffe.

In most of the nuclei that are cut in the proper plane, the indenting droplet appears continuous with the large droplet that fills the cell; in some, however,

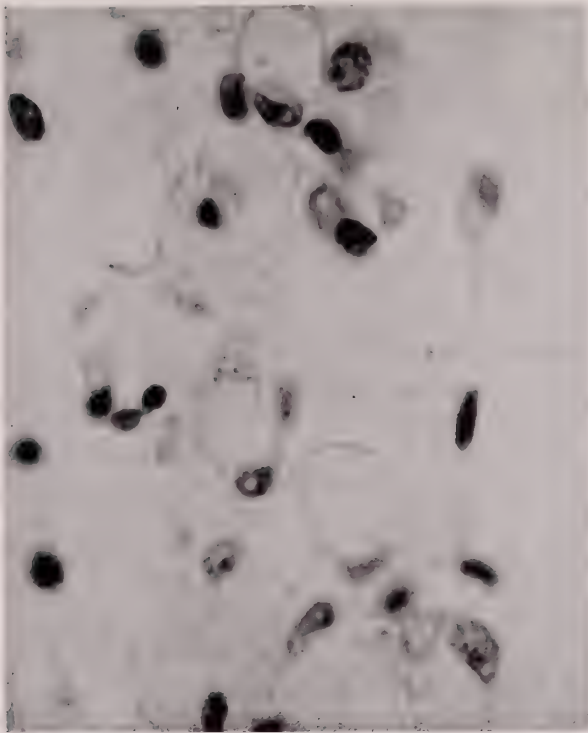


FIG. 10. Atrophic fat tissue from a 45 year old male with extreme emaciation. Three of the fat cell nuclei show "holes" which however are not as sharply outlined as those in normal fat cells. AFIP Acc. No. 151207, Photo. No. 57-1298, H&E 1200 \times .

an unexplained, indistinct, fine curved line seems to separate the two (Fig. 4). Another moot question is the condition of the nuclear membrane surrounding the notch: Is it altered in some way or simply invaginated? A study of such problems with the electron microscope is planned.

It also would be interesting to know whether or not the notching can be observed in explanted adipose tissue, but the one pertinent paper by Burkhardt (10) in which attention is paid to the nuclei made no mention of notches.

A trifling histological detail like a notch in the nucleus did not seem to deserve much attention a few decades ago, especially since it occurred in a tissue that was considered inert. But today's knowledge of the role played by fat tissue in metabolism, and the modern development of cytology and cellular physiology make every detail of the adipose cell a worthy object of study.

Lipid-filled parenchymal cells, in liver or adrenal cortex, for example, can resemble fat cells. The nuclei of such cells are variously formed but are never notched. Only the presence of a characteristic nucleus can tell us that an isolated round space in the adrenal cortex represents a true fat cell and not a "pseudo-fat cell". Such small, round, empty spaces are frequent in the adrenal cortex of man and rabbits.

DISCUSSION

It was neither a chance observation nor the predilection for detail that drew my attention to the nucleus of the fat cell; rather it was a diagnostic need. The study of bone marrow-like (myelo-adipose) structures in the adrenal cortex presented the problem of the origin of single and grouped cells that looked like fat cells. Some authors think that they stem from the reticulum as fat cells do, but others, and by no means less experienced ones, take them to be transformed adrenal cortical cells. Since, as mentioned, lipid-filled adrenal cortical cells and genuine fat cells can look very much alike, a differentiating character was needed, and it was found in the notched nucleus. As early as 1896, only one year after Unna (1) had mentioned and named this peculiarity, Rabl (3) stated that it occurred in fat cells only, and this, to my knowledge, has not been contradicted. Thus, an isolated round fatty space in the adrenal cortex can be recognized as a true mesenchymal fat cell because it carries the characteristic notched nucleus (Fig. 9). The biological importance of this differentiation will be discussed elsewhere.

SUMMARY

1. The nucleus in many—or all—cells of well developed mammalian white fat tissue is notched by a small or large droplet of fat. This was described 50 years ago but still is not widely known.
2. This nuclear characteristic can be used for differentiation between true fat cells and lipid-filled cells of other kinds (pseudo-fat cells).
3. The physiological meaning of the notched nucleus is obscure.

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FATTY LIVER WITH HEPATIC FAILURE IN ALCOHOLICS

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The initial approach of the pathologist is the observation and recording of the structural alterations in diseases. However, only in correlation with the clinical picture become these observations meaningful. Only too often, this correlation is difficult, e.g. if similar structural alterations are associated with different clinical manifestations and functional changes. In this dilemma, three approaches, among others, offer themselves. One is the correlation in a large number of instances to test statistically the validity of an association. The second is the study of the evolution of the disease by serial investigation and here biopsy has not only practical diagnostic but also basic scientific importance. The third is the wilful creation of the structural changes in the experimental animal. Armed with experience thus obtained, the pathologist who started as a descriptive morphologist returns to his anatomical observations to re-interpret them as a correlative biologist explaining the basis of disease. As a tribute to Paul Klemperer as a creative leader in correlative pathology, the relation of fatty metamorphosis of the liver to hepatic failure will be discussed as an example of the cycle just described.

Alcohol abuse is well recognized as one of the main causes of excessive fat accumulation in the liver. Similarly, fatty livers are found in malnutrition, like in gastro-intestinal disease (1) and particularly often in the tropical zone (Kwashiorkor) (2). Hepatic steatosis is also observed in endocrine conditions (e.g. diabetes) (3) and furthermore in congestion, anemia and intoxications (4). However, in the latter instances, it is either transient or associated with other lesions which dominate the clinical and functional manifestations. In contrast, in malnutrition and in alcoholism, fatty liver, being usually persistent, is the most impressive morphologic sign of major significance for the immediate fate and later prognosis. It is seen associated with several clinical features: (1) infections (including pneumonia) explained by the associated disturbance of serum protein formation rendering the body susceptible; (2) central nervous manifestations from either alcoholism (delirium tremens) or Vitamin B deficiency (Wernicke's hemorrhagic encephalopathy); (3) exceptionally acute death explained either by hypoglycemia supposedly resulting from replacement of hepatic glycogen by fat (5) or by fat embolism from the liver (6); (4) cirrhotic manifesta-

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tions including portal hypertension; (5) hepatic failure, sometimes fatal. The last association, especially if accompanied by severe jaundice and encountered with and particularly without cirrhotic features is the poorest understood and the problem of this study.

At the autopsy table, hepatic steatosis associated with jaundice is observed in persons with a history of alcoholism and/or malnutrition in three forms, namely as (1) large fatty liver with virtually intact architecture; (2) florid cirrhosis characterized by beginning obscurity of lobular architecture; (3) septal fatty cirrhosis characterized by destruction of the architecture by fibrosis and regenerative nodules. The second and third forms have been frequently described (7, 8, 9, 10) while the first form, representing an association of severe jaundice with fatty metamorphosis without complicating other lesions, has received less attention (11, 12, 13, 14). It appeared therefore advisable to compare morphologic, clinical and laboratory findings in the three groups in order to establish the validity of coincidences of jaundice and hepatic steatosis, to delineate the entities especially that of large fatty liver with jaundice and to explore the underlying mechanism.

MATERIAL

From the necropsy files of Cook County Hospital, 90 cases were pulled to represent 30 instances each of large fatty liver, florid cirrhosis and fatty septal cirrhosis. All patients conceded alcohol abuse; all were jaundiced, the group with pure fatty liver an average of 12 days, with fatty liver and few regenerative nodules of 16 days, with florid cirrhosis of 42 days and the group with fatty cirrhosis of 31 days. Cases with Wernicke's hemorrhagic encephalopathy, pulmonary embolism, acute nephrosis, intoxications or other obvious causes of death (like severe infections) were excluded. Simple biliary nephrosis was almost always present.

The histologic study included, besides hematoxylin-eosin stains, silver impregnations according to Gomori and aniline blue stains according to Mallory. Fat determinations were carried out by petrolether extraction, the average normal fat content being 4.2 gm per 100 gm wet tissue.

OBSERVATIONS

(1) *Large Fatty Liver*

The green-yellow liver was on autopsy very much enlarged, representing the group with the heaviest weight, occasionally exceeding 4,000 gm. The surface was smooth except for some fibrotic thickening of Glisson's capsule. The anterior edges were blunted. The organ was doughy. On the cut surface, the lobular architecture was as a rule poorly made out without much difference between the centro-lobular and peripheral zones. In some foci it was exaggerated. The portal areas appeared grey-white and slightly enlarged and only exceptionally were regenerative nodules up to 2 mm in diameter seen which were poorly separated from the surrounding parenchyma (Table 1).

Microscopic study demonstrated severe diffuse fatty metamorphosis (Fig. 1A)

TABLE 1

Necropsy findings in patients with various forms of fatty metamorphosis of the liver associated with jaundice

	Large Fatty Liver		Florid Cirrhosis	Septal Cirrhosis
	Without regenerative nodules	With regenerative nodules		
<i>Liver weight in gms</i>				
Mean	2500	2800	2000	2200
Range.....	1800-3500	1800-4300	1500-2800	1900-3800
<i>Spleen weight in gms</i>				
Mean.....	130	150	210	250
Range.....	80-160	90-105	60-315	130-320
<i>Percentage incidence</i>				
Of esophageal varices.....	0	25	30	30
Liver fat in gms %.....	22.0	13.8	7.3	11.2

TABLE 2

Histologic findings in patients with various forms of fatty metamorphosis of the liver associated with jaundice

Percentage Incidence of	Large Fatty Liver		Florid Cirrhosis	Septal Cirrhosis
	Without regenerative nodules	With regenerative nodules		
Central necrosis.....	30	25	33	
Focal necroses.....	20	40	53	56
"Hyaline" bodies of Mallory.....	100	100	80	93
Excessive ductular proliferation.....	10	28	100	100
Fatty cysts.....	70	85	30	100

mostly in the form of large droplets which displaced the flat nucleus to one side and which sometimes coalesced to fatty cysts. The central zone of the lobule exhibited necrosis in about one-fourth of the cases; less than half had focal necrosis with segmented leucocytes replacing liver cells. They were streak-like and extended especially from the portal tracts into the lobular periphery (Fig. 2A). The liver cells, even the fat-containing, varied in size and cytoplasmic staining qualities (Fig. 2B). In large cells with rarefied cytoplasm, protein was coagulated around the nucleus to form ramified "alcoholic hyaline" of Mallory (Fig. 2C). Heavy bile accumulation was reflected in bile pigment staining of coagulated cytoplasm in liver cells, in pigment deposits in Kupfer cells as well as in bile casts or in microcalculi in the ductules which were abundant and frequently dilated, especially in the periportal zone and the portal tracts (Fig. 1BC). Small intraparenchymal bile lakes were common but bile extravasates in the portal tracts were absent. The tracts were slightly enlarged, of stellate shape and infiltrated by histiocytes, lymphocytes and segmented leukocytes, frequently arranged around ductules (Table 2).

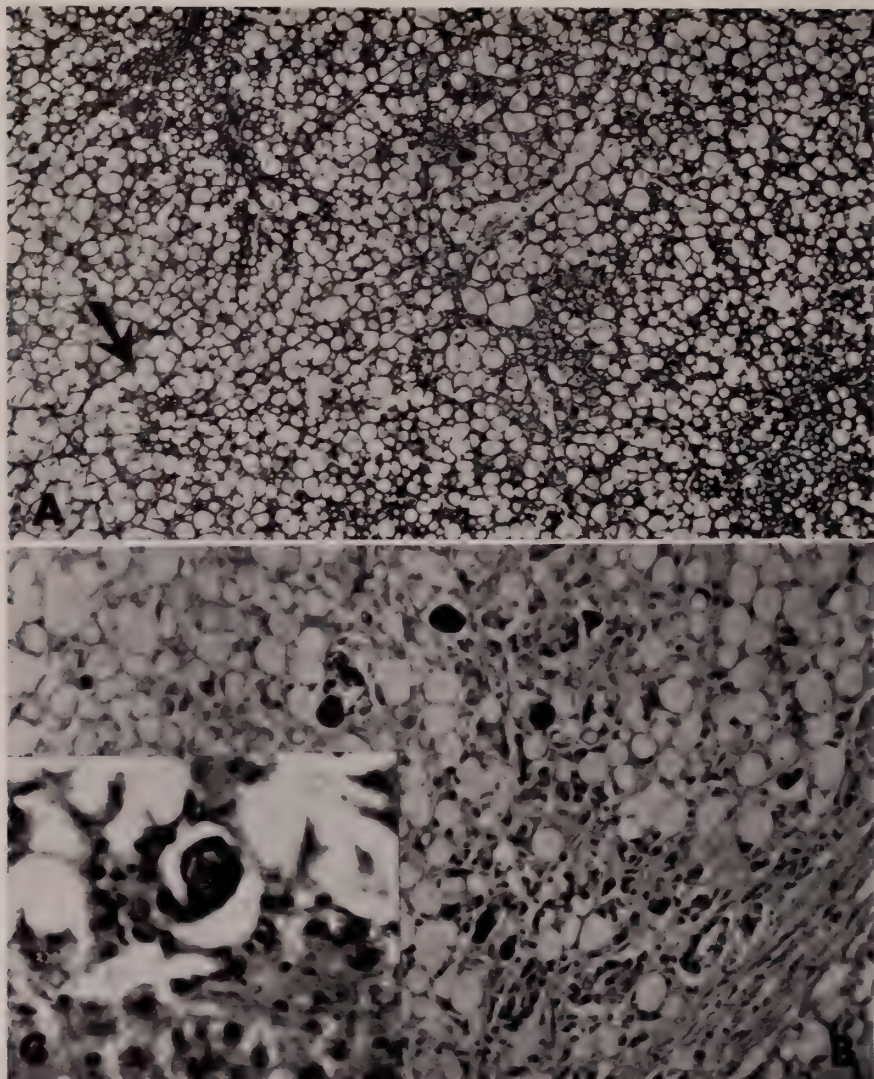


FIG. 1. Large fatty liver with jaundice. A. Large fat droplets in liver cells throughout lobular parenchyma, in places coalescing to fatty cysts (arrow) (100X). B. Bile casts in bile capillaries and microcalculi in proliferated ductules (200X). C. Close-up of same (315X). All H & E.

In 10 of the cases the lobular architecture was intact throughout. In 20, connective tissue septa extended in some areas into the parenchyma and exceptionally linked central and portal canals and in few places regenerative nodules were noted. In both groups liver fat was greatly elevated, more in the first than in the second. The spleen was enlarged in both groups and esophageal varices were noted only in one-fourth of the cases with few regenerative nodules and none in the others. Females were slightly in the majority as were members of the white race although the hospital population consisted to equal degree of colored and

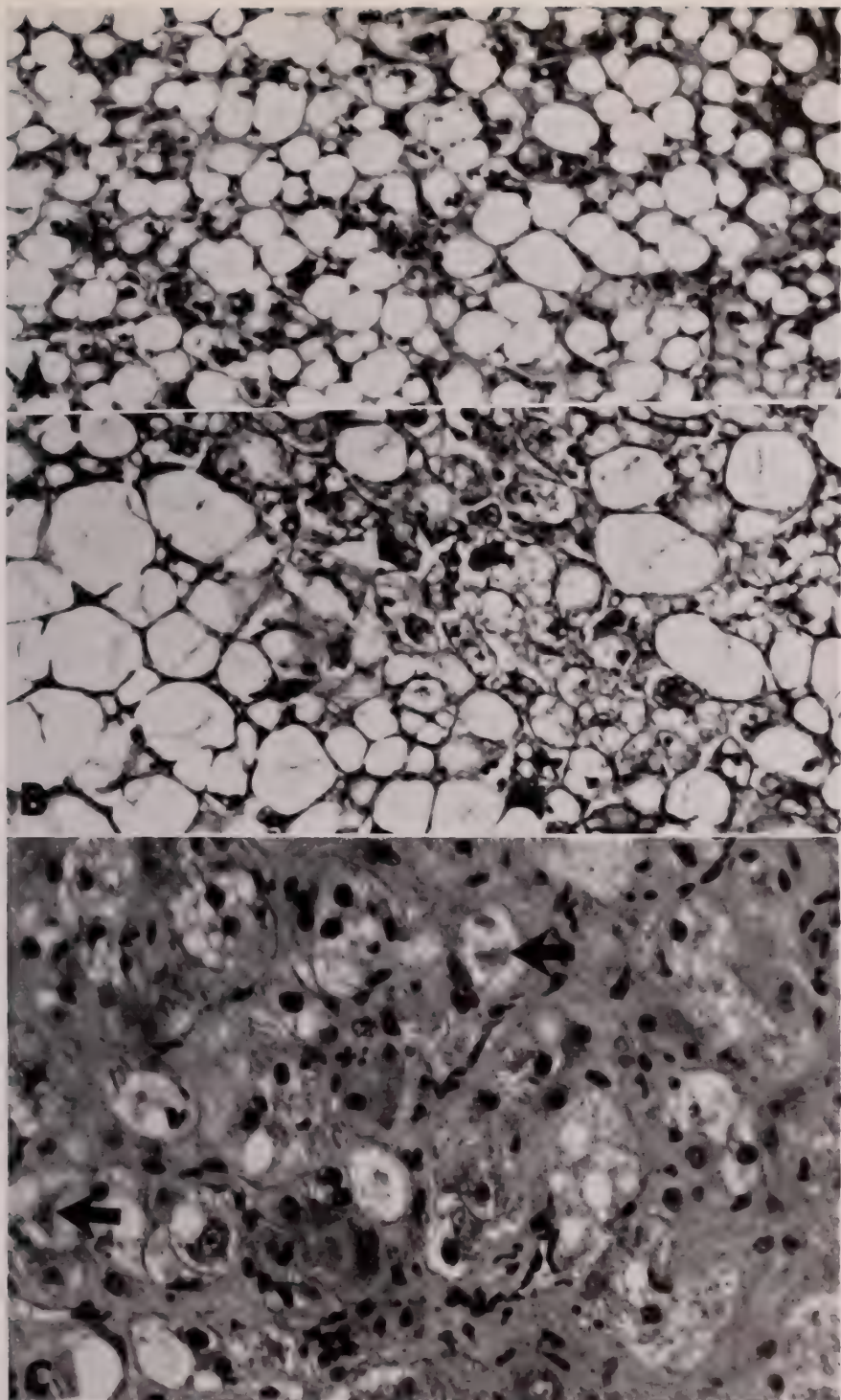


FIG. 2. Large fatty liver with jaundice. A. Segmented leukocytes replacing liver cells which have disappeared (225 \times). B. Irregular staining qualities of the cytoplasm with focal coagulation in fatty and non-fatty cells (225 \times). C. Focal clumping of the otherwise rarefied cytoplasm resulting in "Mallory bodies" (arrows) with accumulation of segmented leukocytes in the vicinity. All H & E.

TABLE 3

Clinical characteristics of patients with various forms of fatty metamorphosis of the liver associated with jaundice

Percentage in	Large Fatty Liver		Florid Cirrhosis	Septal Cirrhosis
	Without regenerative nodules	With regenerative nodules		
Males.....	40	45	63	70
Whites.....	80	60	55	63
Below 35 yrs. of age.....	20	15	12	6
35-50 yrs. of age.....	70	70	66	58
Over 50 yrs. of age.....	10	15	22	36
Ascites.....	10	30	66	72
Edema.....	10	10	36	72
Obesity.....	40	50	33	30
G.I. hemorrhage.....	0	20	25	40

TABLE 4

Laboratory findings in patients with various forms of fatty metamorphosis of the liver associated with jaundice

Percentage of Cases with	Large Fatty Liver		Florid Cirrhosis	Septal Cirrhosis
	Without few regenerative nodules	With few regenerative nodules		
Serum bilirubin above 15 mg %.....	20	35	36	42
Total serum protein below 5.5 gm %.....	20	20	27	42
Serum albumin below 2.5 gm %.....	20	25	33	36
Serum gamma globulin above 1.5 gm %.....	50	65	70	80
Cephalin flocculation above 2+.....	40	80	85	70
Thymol turbidity above 5 units.....	30	55	70	30
Serum alkaline phosphatase above 10 BU.....	30	35	36	46
Anemia below 3.5 million.....	20	25	30	36
Leukocytosis above 12,000.....	30	25	20	20

white persons. A not negligible group was less than 35 and few above 50 years of age (Table 3).

Hyperbilirubinemia was very severe in one-fifth of the cases without and in one-third of those with regenerative nodules. Serum gamma globulin was elevated in more than half of the patients. Cephalin flocculation and thymol turbidity were frequently not elevated while alkaline phosphatase activity was (Table 4).

(2) *Florid Cirrhosis*

The liver was only moderately enlarged and firm. The capsule was smooth. The appearance on outer and cut surface varied in the same liver as well as in different livers greatly in color (from yellow to green to reddish mottled) and lobular architecture (from exaggerated to mainly obscured to focal nodular reconstruction).

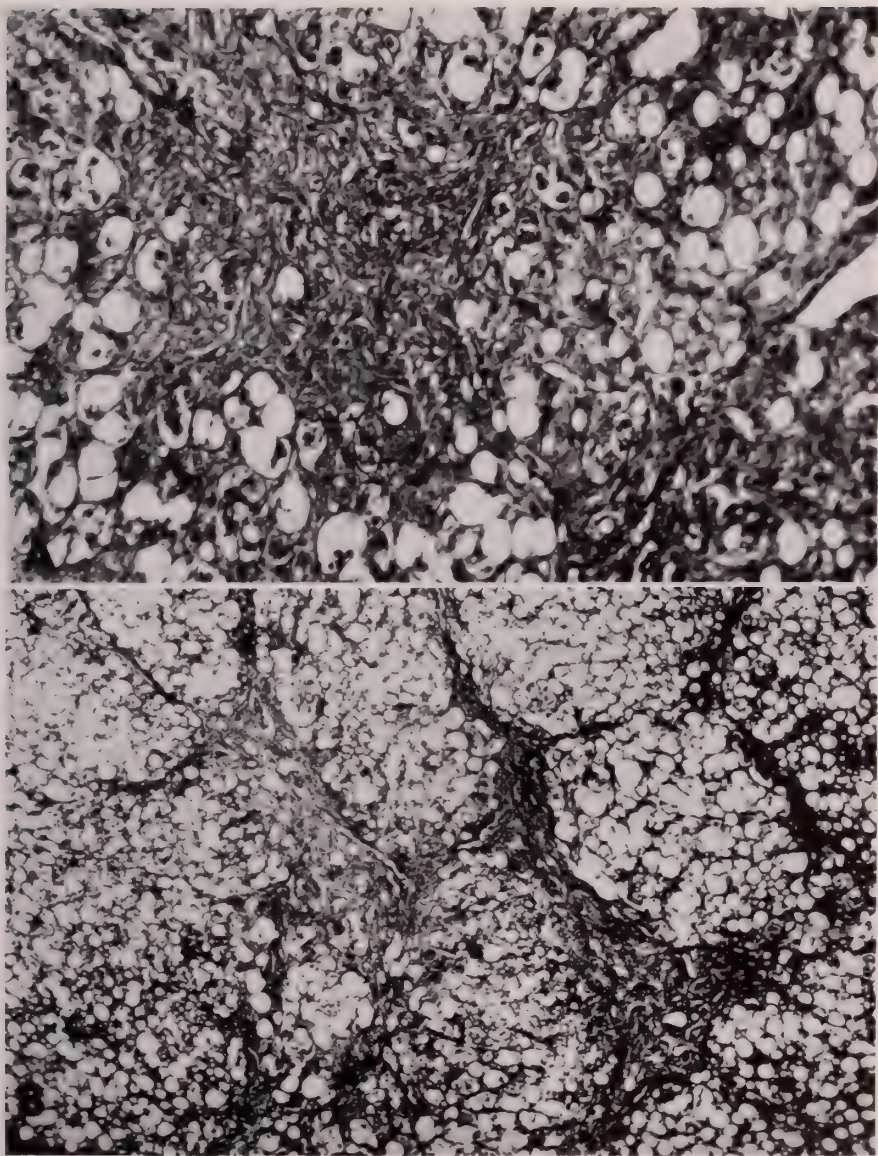


FIG. 3. A. Florid cirrhosis with unsharp border between parenchyma and portal tracts and collagenous membranes radiating into the parenchyma (150X). B. Fatty septal cirrhosis with abolition of lobular architecture by connective tissue septa (100X). Both Mallory's aniline blue.

Microscopically, polymorphism was likewise present. Evidence of bile stasis and cytoplasmic changes were similar to that in the previous group. However, the fatty metamorphosis was patchy and alternated with regeneration which only in places was nodular. Centro-lobular necrosis and inflammatory changes were more conspicuous. The border between portal tracts and parenchyma was

not sharp. In connective tissue stains membranes radiated from the portal tracts into the parenchyma. In places they were condensed to connective tissue septa linking portal with central fields (Fig. 3A). The spleen was usually enlarged and esophageal varices were more frequently found. Male sex and the age group between 36 and 50 years was preponderant. Cephalin flocculation, thymol turbidity and gamma globulin were elevated in the vast majority of cases.

(3) *Fatty Septal Cirrhosis*

The liver was as a rule very large, the average being not quite that of the fatty livers. The yellow to green outer and cut surface exhibited nodules from 2 to 4 mm in diameter and mostly uniform in size and color; only occasionally a larger nodule was deep brown. Connective tissue septa formed a fine white network enforced where it anchored at the larger portal tracts.

Histologically, bile stasis and ductular dilatation and proliferation as well as focal necroses, "hyaline" bodies and inflammatory changes with unsharp borders of the parenchymal nodules were again very conspicuous. Fatty metamorphosis was severe but varied in different nodules while in fat-free areas regeneration was impressive. The center of the lobules was frequently necrotic (Fig. 3B). The spleen was almost regularly enlarged and esophageal varices were the rule. Most patients were white males and more than one-third over 50 years of age. Gamma globulin concentration was high. The thymol turbidity, however, was normal in two-thirds of the cases despite abnormal cephalin flocculation.

DISCUSSION

The frequent coincidence between hepatic steatosis and jaundice with hepatic failure, apparently fatal, as evidenced from observation of a large autopsy material, suggests that the association is not fortuitous. In an autopsy material of chronic alcoholics, out of 162 cases with large fatty liver, 30 had jaundice; of 68 patients with septal fatty cirrhosis, 32 had jaundice, while all cases of florid cirrhosis exhibited it. Of the clinico-pathologic entities encountered, the best known is septal fatty cirrhosis. Florid cirrhosis (10) as not advanced but very active cirrhosis has recently been established whereas the large fatty liver with jaundice, as apparent cause of death, is the least emphasized. The observation of these entities at autopsy raises the question of their relation to each other and the cause of jaundice.

The assumption that the three entities are stages in the fatty liver-cirrhosis syndrome (1) is supported by the increasing average age and evidence of portal hypertension reflected in esophageal varices and splenomegaly in the three groups. The stages of this transition have been pieced together on the basis of autopsy observations in different patients (15). Moreover, the gradual transition of diffuse hepatic steatosis into cirrhosis has been demonstrated by serial biopsy observations in the same patient (16, 12, 17). It has been established also in experimental animals, specifically rats on choline deficient (18) or high fat low protein diets (19, 20). In rats, fatty metamorphosis as such induces cirrhosis (21) because of a peculiar blood supply (22). Most investigators believe that in

humans an added factor is required such as hepatic necrosis to which the fatty liver is more susceptible. Such hepatocellular necroses are observed in the various types of fatty liver associated with jaundice. In this sense, the large fatty liver with jaundice and especially the florid cirrhosis represents a link between steatosis and cirrhosis. In florid cirrhosis, the fat content seems to be secondarily reduced because the starvation in the prolonged disease removes fat from the liver (23).

The jaundice cannot be explained by extrahepatic biliary obstruction nor is it clearly related to the degree of hepatocellular injury. It is therefore mainly an example of intrahepatic cholestasis. The mechanism is probably like in other instances increased permeability of the ductules for biliary substances with inspissation of bile and only secondary periductular reactive inflammation (24). However, the problem of jaundice appears not entirely solved.

Similarly dubious is the mechanism of hepatic failure which is obviously the cause of death since most patients exhibited hepatic coma. Though hepatic necrosis is found in many instances, often only few focal necroses and sometimes, especially in the large fatty liver, none are observed. Moreover, the centrilobular necrosis results probably rather from agonal disturbance of hepatic blood flow than from the disease. The focal necroses may be a reflection of an intercurrent infection. However, they are also seen in rats with fatty liver from low protein high fat diets (25). Fatty metamorphosis as such seems not to interfere with most hepatic functions in humans (12, 17, 1) or in experimental animals (25). Alterations of hepatic circulation which account for hepatic insufficiency in cirrhosis cannot convincingly explain hepatic failure, on an anatomically-demonstrated basis, in the instances without reconstruction. The assumed disturbance of sinusoidal blood flow by fat-laden liver cells (20) has not been confirmed experimentally (26). Since no other disease or intoxication explains the hepatic failure, its mechanism requires elucidation. The relatively high female incidence despite the relatively rare alcoholism in women suggests an endocrine factor.

Of the three clinico-pathologic entities compared, the large fatty liver with jaundice deserves special emphasis despite its unsolved mechanisms. It occurs in relatively young persons of both sexes with some tendency to obesity and with history of alcoholism and or malnutrition. Previous jaundice is usually not recorded. Signs of portal hypertension and ascites are sometimes present as are features of intrahepatic cholestasis reflected in high alkaline phosphatase activity with normal serum flocculation reactions (12, 14).

SUMMARY

Morphologic, clinical and laboratory features were compared in patients dying with fatty metamorphosis of the liver in the presence of jaundice and presumably hepatic failure. The clinico-pathologic entities found were huge fatty liver with or without very few regenerative nodules, florid cirrhosis and diffuse septal cirrhosis. They are stages in the fatty liver-cirrhosis syndrome, the first two representing links between hepatic steatosis and cirrhosis. The jaundice is considered mainly the result of intrahepatic cholestasis. The hepatic insufficiency

cannot always be explained morphologically. Large fatty liver with jaundice occurs in younger persons than nutritional cirrhosis, equally frequent in males and females and is often fatal.

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THE OPERABILITY OF PRIMARY CARCINOMA OF THE LUNG IN RELATION TO HISTOLOGY AND TOPOGRAPHY

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Over thirty years ago Doctor Harry Wessler, who initiated the Division for Thoracic Disease at The Mount Sinai Hospital, recognized the importance of dividing primary carcinoma of the lung into two gross types, the hilar and the peripheral, and described their differing clinical manifestations. He formulated criteria for the radiologic diagnosis of carcinomas originating in the large bronchi at the root of the lung and noted the tendency of these tumors to spread early by way of lymphatics. In contrast, the peripheral or nodular carcinomas tended to remain localized, without much affinity for the lymphatics, even though such a tumor might grow large (1).

These observations led to further studies of the gross pathology, under Doctor Paul Klemperer, in order to gain a more accurate understanding of the manner of growth of the tumors. Clinical and radiologic findings were correlated in an attempt to arrive at a classification which might prove useful in treatment. These studies (2), and later analyses of the findings at operation (3) and the results of resection (4) confirmed the clinical and surgical value of the classification by topography.

About five-eighths of all lung carcinomas were found to originate in the main or lobar bronchi and, with few exceptions, these were found to be of a diffusely infiltrating nature. In only an occasional specimen was a main or lobar bronchial carcinoma found to be fairly well localized. Since such a tumor had invariably produced bronchial obstruction and atelectasis by the time of clinical recognition, differentiation was not possible clinically or radiologically from the tumors which were more diffusely invasive. Of the tumors which originated in smaller bronchi or the parenchyma of the lung, some (about one-third of all peripheral tumors or one-eighth of all cases) displayed a tendency to early and extensive infiltration with diffuse involvement of lymphatic channels; they invaded the peri-bronchial and submucosal lymphatics, the mediastinal lymph nodes and the pleura early in the course of the disease. These tumors also produced nondiscrete poorly demarcated shadows on the roentgen films. With the tumors arising in the main or lobar bronchi, together totaling three-fourths of all the cases, they were considered as *noncircumscribed*. The remaining neoplasms, constituting one-fourth of all cases, were visible radiologically as well demarcated shadows and, therefore, were classified as *circumscribed*.

Classification simply as hilar and peripheral was found to be confusing because some of the circumscribed tumors originating from branch bronchi were seen on roentgen films to be situated near the root of the lung. This simple classification

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was found, also, to be inadequate because it did not mention whether or not the growth appeared circumscribed, that characteristic which was found most to influence the operability of a growth and often the extent of the subsequent surgical procedure.

Admittedly, the topographic classification of these tumors as circumscribed and noncircumscribed on a radiologic basis is not meticulously accurate from a pathologist's point of view but it does characterize the underlying pathology as accurately as possible from the means available before operation or autopsy.

During the intervening years since the earlier reports, in cases totaling many times the number then reported, the topographic classification of carcinoma of the lung has continued to be of inestimable value to us in the understanding of the course of the disease, the symptomatology, the diagnosis, the evaluation of patients for surgery and for estimation of the extent of the surgical procedures required. The percentage distribution of the various noncircumscribed and circumscribed forms has remained quite constant.

HISTOLOGIC CLASSIFICATION

Much attention has been paid of late to discussions of the comparative histology of lung carcinomas in relation to surgical treatment and results. In general, it has been asserted that adenocarcinomas, small-cell carcinomas and anaplastic carcinomas were less often operable and had a poorer prognosis than squamous-cell carcinomas. To some extent such views coincided with our experience. However, we gained the impression that the degree of gross circumscription of the tumor was a better guide to operability of the growth than the cell type alone. To determine whether this was true a study was begun of the histology of the tumors in relation to their operability. We began with the cases which had been reported previously³ in their gross aspects and this is in the nature of a preliminary report.

Two hundred and eighty consecutive cases of carcinoma of the lung were reanalyzed. Of these, seventy-six were excluded because there was insufficient tissue for a precise microscopic differentiation. The study, therefore, is based on two hundred and four cases in which ample material was available for microscopic study.

The neoplasms were divided into the following categories:

- (1) Mature squamous-cell carcinoma.
- (2) Immature squamous-cell carcinoma.
- (3) Anaplastic carcinoma.
- (4) Adenocarcinoma.
- (5) Small-cell carcinoma.
- (6) Miscellaneous histologic forms.

The term "epidermoid carcinoma", in common usage, was not accepted because of the difficulty in classifying the anaplastic carcinomas. Some of them fell into the group of epidermoid carcinomas while the exact classification of others remained open to question. The miscellaneous group was not subclassified because there were few cases in this category.

A *squamous-cell carcinoma* was considered to be *mature* when almost all cells were accumulated in well-defined, discrete islands separated by a thick stroma. In most instances there was hornification of cells within these islands, sometimes with well-defined pearl formation. In many, distinct intercellular bridges could be found.

The tumors were classified as *immature squamous-cell carcinomas* when discrete cell islands were not predominant, although present, and large sheets of squamous cells were evident. The cells were usually larger than in the mature type of squamous-cell carcinoma and hornification and intercellular bridges were rare.

In the *anaplastic carcinomas* there was little or no island formation but the cells were sometimes arranged in sheets suggesting squamous cells. There was, on occasion, question as to the presence of acinar formations suggesting adenocarcinoma. The cells were generally large and the cytoplasm as well as the nucleoli varied greatly in size, shape and staining capacity. In some cases the cells appeared remarkably regular but the nuclei were large and vesicular and contained large nucleoli. These might be considered as the cells of a transitional carcinoma but, because they were not segregated into characteristic structures, they were considered as belonging to the anaplastic group. Even if one were to group them with the other squamous-cell carcinomas, one would have to consider that they represented the most immature type.

The *adenocarcinomas* exhibited distinct acinar formations. In some cases relatively few such acini were discovered but these were included among the adenocarcinomas together with those which consisted entirely of gland formations.

The *small-cell carcinomas*, often classified as anaplastic carcinomas, were considered as a separate group. They consisted entirely of small cells, either round or oat-shaped, or both, almost always with deeply stained nuclei and scanty cytoplasm. The masses of cells were not demarcated into islands or distinct cell groups. The stroma was scanty and irregularly distributed.

The miscellaneous group were few in number and included papillary carcinomas, tumors in which the cells were arranged in rows of columnar cells and those consisting of mucous cells without acinar formation.

OPERABILITY OF PRIMARY CARCINOMA OF THE LUNG

The term "operability", when applied to a malignant neoplasm, may be used in different ways. For our purpose, which is to determine whether a reliable clue can be obtained as to whether a patient with a carcinoma of the lung can be cured of the disease by a surgical operation, the term "operable" is used to indicate that recurrence of the tumor within the chest is not to be expected after its removal. Thus far, our experience has led us to believe that extremely few patients are cured by even a radical pneumonectomy. For the purposes of this study, therefore, we have considered as inoperable those cases in which the mediastinal lymph nodes were found to be involved even though a more or less radical resection was performed. On the other hand, the cases in which only the lymph nodes within the lung root were involved were considered operable if they

were removed together with the diseased lung. Similarly, circumscribed tumors locally invading the chest wall, diaphragm or pericardium were considered operable if the entire lesion with the invaded structures was resectable and mediastinal lymph nodes were not involved.

There were one hundred fifty seven instances of noncircumscribed neoplasm and forty seven of the circumscribed type. Of the forty seven circumscribed tumors, twenty nine or sixty two percent appeared to be operable on clinical grounds. Seven were not operated on for various reasons not concerned with the neoplasm, leaving twenty two in which surgical exploration was carried out. Of these, seventeen or seventy seven percent proved operable. On the other hand, of the one hundred fifty seven cases of noncircumscribed carcinoma, only fifty six or thirty five percent appeared operable clinically. In twenty three of these operation was not performed and of the remaining thirty three sixteen, or somewhat less than fifty percent, proved to be completely removable at operation. These figures indicated that operability was related to the circumscription of the tumor.

CELL TYPE IN RELATION TO OPERABILITY

The results of the study of the cell type alone in relation to operability indicate that the distinctly squamous-cell carcinomas are more likely to be operable than the adenocarcinomas and the small-cell or anaplastic carcinomas. This is in agreement with general opinion. However, an entirely different concept is obtained when the histology is considered together with the gross topography of the neoplasm.

Table I represents an analysis of the operability of the noncircumscribed carcinomas in relation to the cell types. Table II represents a similar analysis of the circumscribed carcinomas. A comparison of the two groups with an estimate of the operability according to histology in each group is given in Table III. Here a wide discrepancy is noted in the two groups in the operability of the tumors generally considered to have the poorest prognosis, namely adenocarcinomas, small-cell carcinomas and anaplastic carcinomas. Only 2 percent of these tumors

TABLE I
Operability of noncircumscribed carcinoma according to histology

Histologic Cell Type	Removed at Operation	Considered Removable Clinically But not Operated	Not Removable At Operation	Considered Not Removable Clinically	Total
Squamous mature.....	10	9	8	10	37
Squamous immature.....	3	7	4	31	45
Anaplastic.....	0	2	1	18	21
Adenocarcinoma.....	0	0	0	9	9
Small-cell.....	1	3	3	29	36
Miscellaneous.....	2	2	1	4	9
Total.....	16	23	17	101	157

TABLE II
Operability of circumscribed carcinoma according to histology

Histologic Cell Type	Removed at Operation	Considered Removable Clinically But Not Operated	Not Removable At Operation	Considered Not Removable Clinically	Total
Squamous: mature.....	8	1	0	4	13
Squamous: immature....	3	2	1	2	8
Anaplastic.....	3	1	0	4	8
Adenocarcinoma.....	2	0	2	6	10
Small-cell.....	1	1	1	1	4
Miscellaneous.....	0	2	1	1	4
Totals.....	17	7	5	18	47

TABLE III
Comparison of operability of circumscribed and noncircumscribed carcinoma

	Circumscribed	Noncircumscribed
Mature squamous.....	69%	40%
Immature squamous.....	46%	13%
Anaplastic carcinoma.....	24%	2%
Adenocarcinoma.....		
Small-cell carcinoma.....		

proved operable in the noncircumscribed group whereas 24 percent or ten times as many, proved operable when the tumors appeared circumscribed on the x-ray films. In the cases of immature squamous-cell carcinoma the circumscribed tumors proved operable more than three times as often as the noncircumscribed. A considerably smaller difference was noted in the cases of mature squamous-cell carcinoma.

GRADING OF THE NEOPLASMS IN RELATION TO OPERABILITY

An attempt was made to determine whether any other index of the comparative malignancy of a neoplasm could be correlated with operability. First, the frequency of mitoses did not appear to be related to operability in this series. Second, depending, as it does, on the degree of differentiation of the tumor cells toward or from the normal tissue as an index of prognosis, Broders' classification could not be applied logically because of the digression of these tumors, especially the squamous-cell carcinomas, from the normal tissue of the bronchial mucosa and, also, because of the marked tendency to pleomorphism in all lung carcinomas. The normal bronchial lining is stratified columnar epithelium. The change to squamous epithelium per se indicates a pathological process. However, an attempt was made to classify the squamous cell carcinomas and the adenocarcinomas according to other normal similar tissues. While it is true that epithelial pearls were found predominantly in the tumors classified as mature

squamous their frequency in these and the other squamous tumors was not such as to permit very effective grading. In the small series of adenocarcinomas no apparent correlation could be noted between the grading and the operability. *Grade IV cases proved operable when the tumor was circumscribed and tumors of Grade I uniformly proved to be inoperable when the tumor was of the noncircumscribed type. All the anaplastic and small cell tumors would be Grade IV, according to Broders' method, yet a significant number were operable when the tumor was circumscribed.*

DISCUSSION

We consider that the histologic classification we have selected is a most useful one. It is simple and the various cell types are well recognized by all pathologists so that there is little difficulty in classifying each case. That there is a relationship between the cell type and operability in both gross categories is clearly indicated by Table III which shows progressive diminution in the operability of the three main groups, namely the mature squamous, the immature squamous and the one consisting of adenocarcinomas, anaplastic and small-cell carcinomas.

The importance of considering the gross circumscription of the tumor as well as the histology is evident from the report by Aufses (4) which concerned the ultimate prognosis of patients who had been operated upon and the tumors removed. In his series, fully sixty two percent of the patients with adenocarcinomas of the grossly circumscribed type survived five years after resection. This single observation proves that the tumor cell type by itself is not the determining factor in operability.

The biology of the neoplasm, in particular its tendency to spread to other tissues, is the important factor to be considered. While the constituent cell type of the growth is in some degree related to this tendency to spread, other as yet unknown factors undoubtedly operate to produce the difference in the behavior of neoplasms of the circumscribed and noncircumscribed type with the same microscopic appearance.

This study has shown that although adenocarcinomas, anaplastic carcinomas and small-cell carcinomas rarely proved operable when they occurred as non-circumscribed tumors, they frequently proved operable when they formed a nodular or circumscribed growth. Neoplasms with most immature-appearing constituent cells often grow largely by expansion and fail to infiltrate the surrounding tissues widely. They may lend themselves, therefore, to complete and successful surgical extirpation regardless of their histologic character.

In the last analysis, the manner of its growth rather than its cell type is the most useful measure in determining the operability of a lung carcinoma and this is best judged by the gross appearance. Fortunately, the tendency or lack of tendency to spread is visible on the roentgen films. The tumor is seen to grow locally and to present itself as a fairly well circumscribed shadow. It is obvious that it has less tendency to spread than if it is seen to infiltrate the surrounding tissues extensively.

SUMMARY

1. Two hundred and four cases of carcinoma of the lung were studied from the standpoint of operability in relation to the histology of the neoplasm and its gross topography.

2. There was a relatively high incidence of operability in the cases of mature squamous-cell carcinoma whether they were circumscribed or noncircumscribed. However, the incidence of operability was greater in the circumscribed type.

3. The immature squamous-cell carcinomas also proved operable in a large percentage of the circumscribed tumors but not in the noncircumscribed.

4. Adenocarcinomas, anaplastic and small-cell carcinomas rarely proved operable when the growth was noncircumscribed but were frequently operable if the tumors were grossly circumscribed.

5. The circumscription of the tumor and its growth in the form of an expanding nodule is a manifestation of a restriction in its tendency to spread, and of its operability, regardless of the constituent cell type.

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AN INJECTION MASS OF MAXIMAL RADIOPACTY FOR POSTMORTEM ANGIOGRAPHY

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AND

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In a recent communication Schlesinger described a radiopaque mass for the postmortem injection of blood vessels (1). The gelatine menstruum of the mass was buffered at pH 6.2. It was made to stay liquid at room temperature by potassium iodide and was rendered radiopaque by barium sulfate. The addition of formalin in adjusted concentrations just prior to injection allowed for intravascular conversion of the mass into an irreversible gel after a predetermined interval of time. Generally a period of about 1 hour was preferred. The casts so produced were flexible and facilitated greatly the dissection of the vessels with scissors, in the fresh specimen. If the organ was injected via two or more of its constituent arteries with masses tinted differently with water soluble dyes the presence or absence of collaterals could be established by observing the color of the casts and the imparted staining of the vessel intima.

The mass had additional desirable properties among which were the following: 1) It gave reproducible results; 2) it yielded permanent X-ray records of the injected vessels; 3) it did not cross the capillary bed; 4) it did not impair the gross or microscopic appearance of the tissues.

The present modification was developed because of the need for an injection mass of distinctive radiopacity which would allow for differential identification on the X-ray film when used in conjunction with the original Schlesinger mass. Among other issues under investigation we desired information on certain questions of collateral circulation concerning sizes and sites of anastomoses not accessible to dissection with scissors. Because we wished to duplicate the desirable qualities of Schlesinger's mass as enumerated above, the problem was approached in principle by adding to its basic formula substances of very high radiopacity. Metallic mercury was found best among several substances tested.

PREPARATION OF INJECTION MASS

Ingredients:

1. 2-Octanol (Secondary n-Octyl Alcohol)
2. Phenol, U.S.P. liquified
3. Bacto-Gelatin (Difco Laboratories)
4. Potassium Iodide, U.S.P., granular

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5. Harleco Buffer Salt Mixture (Potassium Phthalate and Sodium Phosphate) pH 4.2
6. Barium Sulfate, U.S.P. Merck. "Suitable for X-ray Diagnosis".
7. Mercury, triple distilled

Stock Mixtures:

Mixture A:

2-Octanol (# 1)	20 cc.
Phenol (# 2)	30 cc.

Mix well and keep in bottle fitted with calibrated dropper.

Mixture B:

Gelatin (# 3)	230 gm.
Potassium Iodide (# 4)	345 gm.
Buffer Salt Mixture (# 5)	46 gm.

Mix this powdery mixture thoroughly.

Mass C (Modified Schlesinger's Gelatine-KI-Barium Sulfate Mass)

Place 163 cc. of distilled water in Waring Blendor.

Add 1 cc. of Mixture A.—Spin for 1 minute.

Add 61 gm. of Mixture B.—Spin for 1 minute.

Add 100 gm. of Barium sulfate (# 6).—Spin for 2 minutes at "High Speed."

Store Mass C in stoppered Erlenmeyer flask at room temperature. Let stand for 24 hours before use.

Gelatine-KI-Emulsion

Place 82 cc. of distilled water in Waring Blendor.

Add 0.5 cc. of Mixture A.—Spin for 1 minute.

Add 31 gm. of Mixture B.—Spin for 1 minute.

Store in stoppered Erlenmeyer flask at room temperature.

Mass D (Mercury-Gelatin-KI-Mass)

To 20 cc. of the Gelatin-KI-Emulsion add 20 cc. by volume of Mercury (# 7)
Place in Monel Metal Jar (semi-micro size) and spin at "High Speed" for 3 minutes.

Store Mass D in stoppered flask at room temperature. Let stand for 24 hours before use. Mass D becomes alkaline within 24 hours.

Final Injection Mass:

Mass E (Mercury-Gelatine-KI-Barium Sulfate Mass)

Shake Mass C and Mass D thoroughly.

Pour 45 cc. of Mass C into an Erlenmeyer flask.

Add 5 cc. of Mass D.

Stopper and shake vigorously by hand until the mass is a uniform gray.

Mass E should not be constituted until the day of injection. In practice we keep on hand several 45 cc. units of Mass C in graduated mixing cylinders which are kept stoppered. To each are attached two stoppered test tubes, one containing 5 cc. of Mass D and the other 5.5 cc. of formalin, the concentration of formalin depending on the Viscosity Conversion Concentration described below.

= 30 cc. of formaldehyde solution, U.S.P. plus 70 cc. of distilled water; 40% formalin = 40 cc. of formaldehyde solution, U.S.P. plus 60 cc. of distilled water, etc.). Invert each tube *immediately* after addition of its respective formalin dilution using a rubber stopper. Into each tube a wooden applicator is inserted. Every 5–10 minutes and for a period of 45–60 minutes withdraw the applicator and observe the liquidity of the mass dripping from it. That concentration of formalin which renders the mass sticky and tenaceous after about 30 minutes constitutes the Viscosity Conversion Concentration of formalin for the particular batch of mass (in our laboratory usually between 40 and 60%, depending on room temperature). Complete solidification will take place in another 15–30 minutes. This test tube experiment approximates the subsequent behavior of the mass in the injected vessels. Although the choice of 30 minutes following the addition of formalin is arbitrary it is a practical value within which to complete any subsequent vascular injection. Moreover, the time limit is short enough to prevent sedimentation of the mercury droplets inside the vessels thus avoiding uneven X-ray shadows.

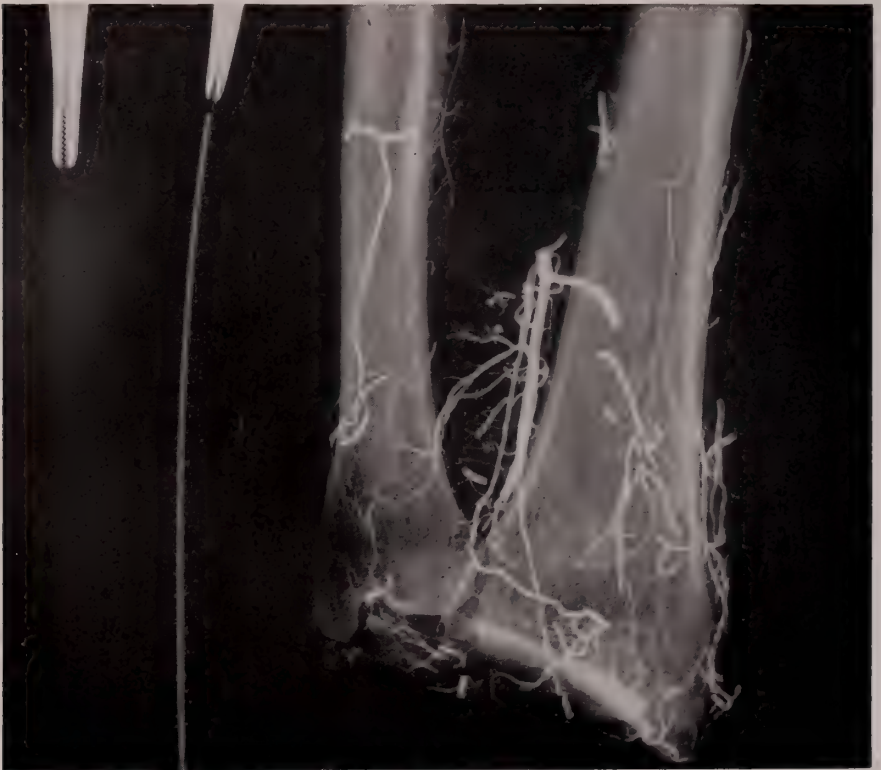


FIG. 1. Distal part of a human forearm (amputation specimen). Mass E was injected into the brachial artery at 200 mm. Hg. The X-ray picture reproduced was taken after the soft tissues had been dissected off. Note the distinctiveness of the vessel shadows against the bone.

B. Hydrogen Ion Concentration:

Whereas the hydrogen ion concentration of Mass C is quite constant (pH approximately 4.6) the addition of metallic mercury (Mass D) initiates a reaction between Hg and KI with the production of KOH. It was for the purpose of reducing this alkalinity that the buffer of the Schlesinger formula was not only doubled in amount but also changed from one of pH 6.2 to one of pH 4.2. Nonetheless, the hydrogen ion concentration of Mass E slowly changes toward alkalinity as shown in Table 1. The rate of this change cannot be retarded by storing Mass E at icebox temperature. However, Table 1 also demonstrates that the initial pH of Mass E will be consistently at about 4.8 provided its constituent Masses C and D are not combined until the day of injection. Under these conditions the viscosity conversion concentration of formalin once determined for a particular batch of injection mass remains valid for a period of at least 2 months provided no great change from the room temperature of the original test has taken place.

C. Viscosity:

As determined in Ostwald-Fenske Viscometers at 25°C Mass E is approximately 10 times and Schlesinger's mass several hundred times more viscous than heparinized normal blood (5 centipoises under the same conditions). The variations in the values obtained for the same mass in viscometers of different bore reflect the non-Newtonian character of the masses.



FIG. 2. Heart, right ventricle. The right coronary artery (ostium, at arrow) was injected with Schlesinger mass. However, its second branch occluded at the origin had become filled with Mass E injected simultaneously into the left coronary artery. (BH A-57-17)

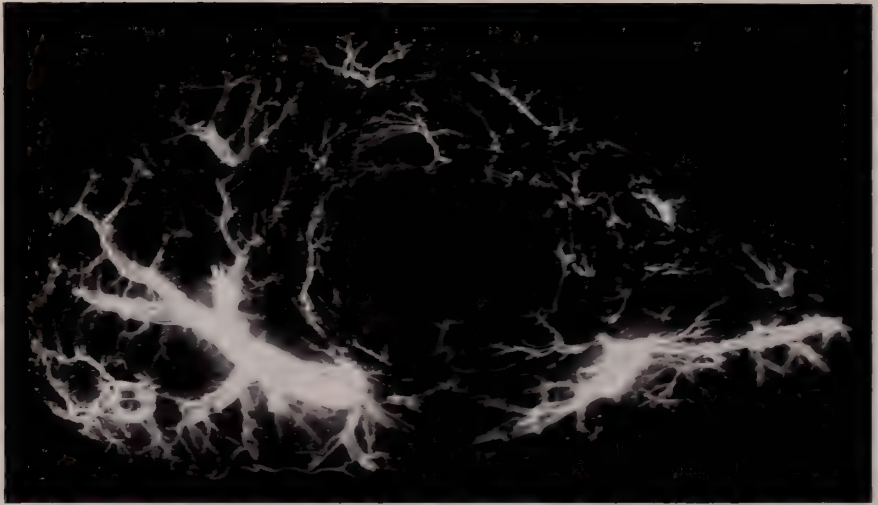


FIG. 3. Slide of human liver containing a centrally liquefied metastasis of a bronchogenic carcinoma. Injection of hepatic artery with Mass E was followed by injection of the portal vein with Schlesinger mass. Although photographic reproduction of this type of preparation is difficult it is possible to distinguish arteries and veins in the lower half of the photograph. (BH A-56-77)

A disadvantage of the low viscosity of Mass E is that leakage from the cut edges of the specimen is more difficult to control than leakage of the highly viscous Schlesinger mass. Any leakage not amenable to clamping may be stopped by the application of pledgets soaked in solutions of sodium or potassium hydroxide because strong alkali greatly hastens the conversion of formalinized gelatine from a sol to a gel.

D. Penetration:

The hearts of man and pig were chosen as test organs for studying vascular penetrability. When injected at 200 mm. Hg both the Schlesinger mass and Mass E are found quite regularly in vessels having an internal diameter of 20-25 micra (as measured in paraffin sections). Vessels smaller than that are filled irregularly and capillaries are not filled at all. When injected into a single coronary

TABLE 2

Specific gravities and viscosities in centipoises. The viscosities were determined with graded Ostwald-Fenske Viscometers, at 25° C.

Approximate Capillary Bore of Viscometer, in mm.	Viscosities in Centipoises		
	Mass C Sp. Gr. 1.510	Mass E Sp. Gr 2.096	Schlesinger Mass Sp.Gr. 1.480
1.0	52.9	50.5	
1.25	60.6	54.8	
1.85			3770
2.80			1903

artery of the pig heart Mass E appears in the uninjected coronary artery more frequently than does the Schlesinger mass. However, the quantities transmitted do not amount to more than a faint trickle with either mass.

COMMENT

The injection mass here presented is of vastly greater radiopacity than the Schlesinger mass from which it is derived. It may be recommended whenever a particularly high radiocontrast is desired as for instance in vascular injection studies of specimens containing bone. For the same reason it should prove of value in the postmortem angiography of bones themselves (Fig. 1).

The distinctive radiocontrast of Mass E is obvious even in vessels as small as 150–200 micra, i.e. in the smallest twigs still visible on the X-ray film. By injecting respectively Mass E and Schlesinger's mass into the right and left coronary arteries we have been able to establish not only the presence or absence of inter-coronary anastomoses but also their precise sites and diameters (Fig. 2). Valuable, too has been this combined use for stereoscopic angiography of organs having a dual arterial blood supply such as liver and lung (Fig. 3). The use of the Mercury mass (Mass E) in conjunction with the Schlesinger mass may be objected to by reason of the marked differences in their viscosities. If so, one may substitute the latter with Mass C of the present report which has roughly the same viscosity as Mass E (Table 2) yet the same radiocontrast as Schlesinger's mass. Of course, the Viscosity Conversion Concentration for Mass C has to be established separately by the procedure previously outlined. In our hands, only 80–100% formalin were useful concentrations.

The present mass does not interfere with the preparation of microscopic sections. When used in conjunction with either Mass C or with Schlesinger's mass it can be easily distinguished microscopically by virtue of its black mercury droplets.

SUMMARY

A radiopaque mass for postmortem angiography is described. Its exceptional radiopacity makes it useful for the injection of bones and bone containing tissues. It has been employed to advantage in conjunction with the less radiopaque Schlesinger mass to determine sizes and sites of collaterals. The two masses have also been used to identify separate vascular systems of organs with dual blood supply, such as liver and lung. The mass does not usually extravasate or cross the capillary bed.

ACKNOWLEDGMENT

We wish to thank Dr. A. S. Goldberg, Biochemist at The Bronx Hospital for the viscosity determinations.

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HISTOLOGIC SEQUELAE OF HORMONE THERAPY AND HYPOPHYSECTOMY IN BREAST CANCER

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While the consequences of hypophysectomy, especially its ability to modify pre-existing tumors, have been very well investigated both experimentally and clinically, the histomorphological effect of this procedure, especially in man, seems to have aroused but little interest.

This is the more regrettable since hypophysectomy is playing an important role in the treatment of hormone-dependent malignant neoplasms. The purpose of this paper is to describe the morphological findings in a single case. Although seven cases of malignancy treated by hormone therapy combined with hypophysectomy were observed (six female breast cancers and one cancer of the penis) restrictions on space make it preferable to confine the report to the findings in one patient:

CASE REPORT

A white female, born 1891, was seen on 10/30/51 at the tumor clinic with a mass in the left breast, of about 16 months' duration. It gradually increased in size till the upper outer quadrant was replaced by a large fungating mass, measuring about 10.5 cm. It was deeply ulcerated and smelled badly. There were multiple nodules in the skin over the left trunk, enlarged firm nodules in the left axilla and questionable ones in the left infraclavicular region. A biopsy was performed and revealed the epidermis to be slightly hyperkeratotic. There was intercellular edema in the stratum germinativum and flattening of the rete ridges. At one edge the epidermis was thinned and exhibited spongiosis and vesicle formation. The latter were often filled with an eosinophilic coagulum. In about five per cent of the cells of the stratum germinativum which were examined, sex chromatin was present. The dermis was edematous and invaded by solid cords and nests of poorly differentiated cells, characterized by marked poly- and hyper-chromasia, with distinct variation in size and a moderate number of mitoses per high power field. Sex chromatin was observed in some of the tumor cells. Associated with this carcinomatous infiltration was a moderate inflammatory reaction. Diagnosis: poorly differentiated solid carcinoma (see Fig. 1).

The patient was referred to the endocrine clinic for androgenic therapy and started receiving implants on November 1, 1951. After two weeks there was considerable regression of the tumor, and the ulcerations became clean and covered by new epithelium. Implantation was continued every two weeks and by December 20, 1951, there was "definite healing and remarkable new epithelization of all ulcerated areas with distinct shrinkage of all lesions of the left breast."

On June 17, 1952, her case was reviewed in the tumor clinic and improvement of the initial lesion was observed. In the meantime, skin nodules began appearing which were extremely firm and pruritic, and were spreading throughout the scalp, neck and trunk. Another biopsy yielded the following picture: Slight acanthosis of the epidermis and scanty

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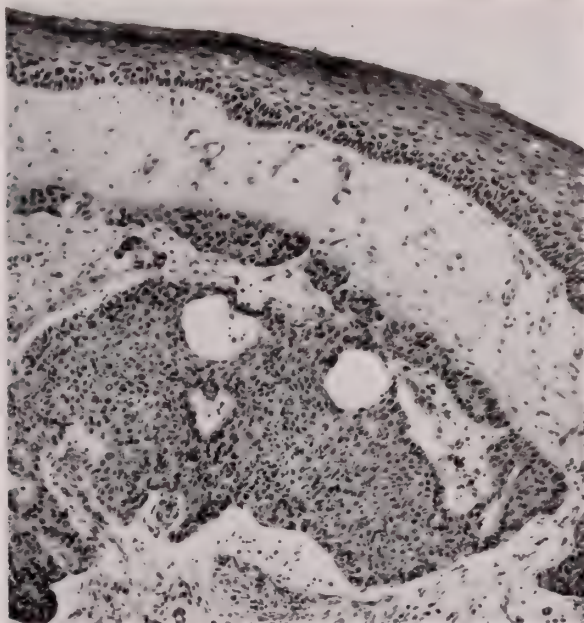


FIG. 1. Poorly-differentiated carcinoma of the breast invading skin. H & E $\times 111$ S-6128-51.

perivascular lymphocytic infiltration in the superficial dermis. In contrast to the first biopsy, the tumor cells were arranged in very small groups and slender cords, surrounded and compressed by dense strands of collagen and connective tissue, representing a well-marked desmoplastic reaction. The tumor cells showed only rare mitoses, moderate pleomorphism and polychromasia, with evidence of rhexis and pyknosis. Sex chromatin was present in the epidermal cells as well as in some of the tumor cells. Diagnosis: Skin metastases of scirrhous carcinoma (see Fig. 2).

Facial hirsutism began appearing by mid July, 1952, after she had received 100 pellets, or 7.6 grams of testosterone implants. The latter were given then four or more weeks apart. By December, 1952, there was recurrence of the ulceration of the initial lesion, and severe anemia developed. She began losing weight and feeling weak, although generally better than before the implants. By February, 1953, one of the skin nodes in the left flank began to ulcerate, implants were stepped up again and she again responded with shrinking of the nodules and the primary mass, which lasted for about three months. She continued going downhill with severe hemorrhage from the tumor mass. The giving of oral estrogen did not produce any significant change.

She continued to worsen and was scheduled for hypophysectomy. After due preparation surgery was performed on August 7, 1953. She withstood the procedure fairly well and returned to the recovery room in satisfactory condition. During the postoperative period, starting within 24 hours after surgery and continuing until her sudden death six days later, it was observed that the skin metastases all over her body became extremely soft and many were cyanotic.

Autopsy Abstract: The body is covered with nodules of varying consistency and size, ranging from several mm. to 3 cm. in diameter. Some are umbilicated. There is a large ulcerated fungating tumor mass on the anterior surface of the left chest, measuring about 22 x 14 cm. and elevated about 2 cm. above the skin

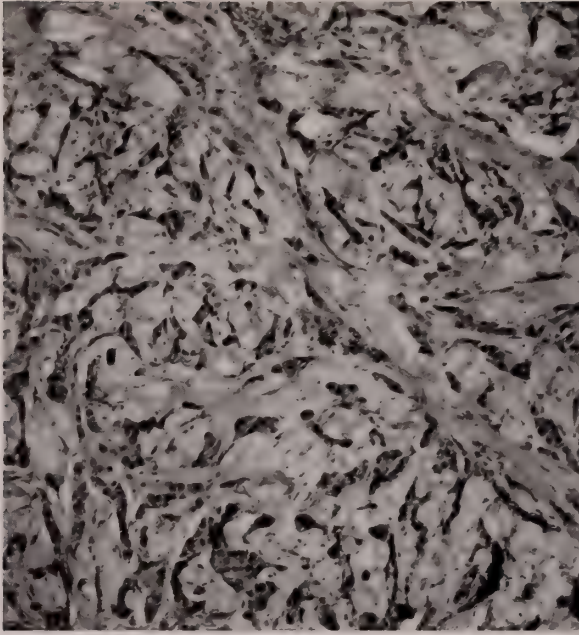


FIG. 2. Same case as Fig. 1 following androgen therapy, now scirrhus in pattern, removed from primary tumor. H & E $\times 122$ S-3467-52.

surface. The pubic hair extends upwards to the tip of the xiphoid process; a well-developed beard is noted.

The anterior part of the pituitary fossa is filled with blood clot posterior to which is a small excavation 5 mm. in diameter and about 2 mm. in depth. There seems to be a 1 mm. rim of intact pituitary left.

The large tumor mass in the breast does not extend into the pectoralis muscles. It is rather soft and brownish-grey throughout. The axillary lymph nodes are enlarged, somewhat firm and show a greyish-white cut surface. Numerous firm, white nodules ranging from several mm. to 1.5 cm. dot the surfaces of both lungs and the left parietal pleura; many have soft centers.

On opening the heart and the large vessels, a pulmonary embolus in the main trunk is noted, which originated from a thrombosis of the right femoral vein. Near the apex of the posterior wall of the left ventricle, there is a small white tumor nodule.

The liver contains numerous metastases, most of them exhibiting a soft center. Adrenals are grossly without pathology. The remainder of the body shows no findings pertaining to this discussion.

Microscopic Examination: The histological picture of the skin metastases vary according to their gross appearance. The soft hemorrhagic ones exhibit almost complete necrosis of the dermis and the former tumor pattern presents itself as ghost outlines in which, sometimes, the difference between tumor plugs and stroma is just discernible. Very often only the preservation of the covering

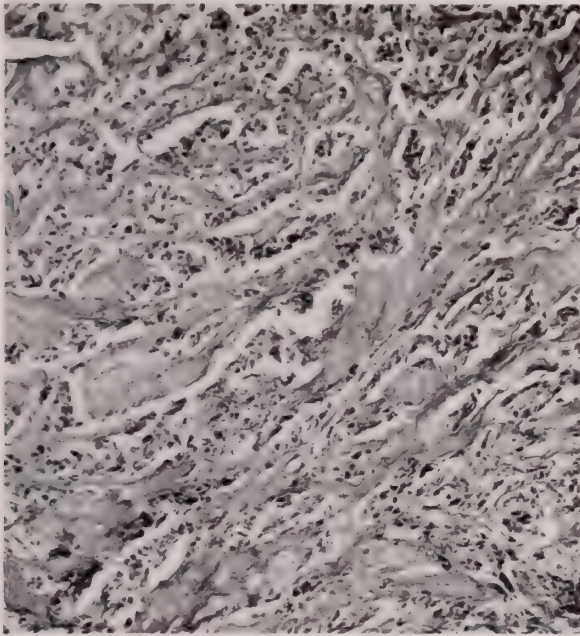


FIG. 3. Skin metastases from autopsy of same case. Extensive necrosis with remnants of tumor tissue. H & E $\times 122$ A-473-53.

epidermis makes it possible to identify the origin of the preparation (see Fig. 3). In the epidermis covering the necrotic areas, in surviving tumor cells in other organs and also in the adrenal cortex, the presence of sex chromatin can be demonstrated (Fig. 4).

Some other skin metastases show a mixture of necrosis and hemorrhage with remnants of islands of tumor tissue at the periphery. These tumor islands show either the character of a poorly-differentiated solid carcinoma, as described in the first biopsy, or the more scirrhous type described in the second biopsy; some have a mixture of both. There are also metastases without necrosis and hemorrhage which offer one of the two histological patterns or a combination of both. The metastases in the lung show similar pictures, but here numerous areas of scarring are noted, either free of tumor or scirrhous in type, or re-infiltrated by plugs of poorly-differentiated carcinoma cells. In other places there are extensive areas of tumor infiltration with the cribrous pattern frequently met with in cancers of breast and prostate, and associated with it are deposits of lime salts (psammoma bodies).

The metastases in the liver are mainly of the solid, immature type and exhibit extensive central necrosis. The cortex of each adrenal shows islands of necrosis, hemorrhage or both. Numerous sections obtained from the primary tumor in the breast show the pattern of a solid, poorly-differentiated carcinoma. Examination of the remnant of pituitary reveals that most of the residuum of the anterior lobe is completely replaced by necrosis, hemorrhage and an infiltra-

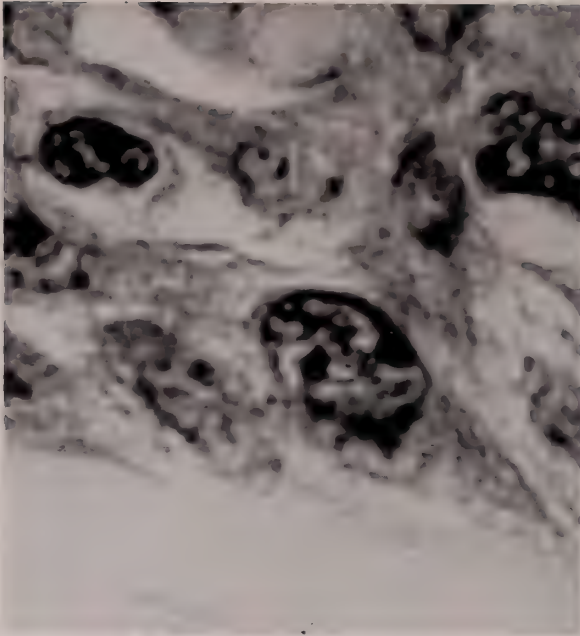


FIG. 4. Sex chromatin H & E. Found in nuclei in cells of skin, adrenal cortex, and in some of the tumor cells before treatment, after androgen therapy, and in skin (after death) covering necrotic metastases. \times 3338 S-6128-51.

tion of polymorphs. The remainder of the anterior lobe shows microscopic hemorrhages, and a rim of well-preserved tissue about twenty cells deep, predominantly eosinophile.

DISCUSSION

If we screen the available literature with reference to histological evaluation and comparison of tumor pattern prior to and following hypophysectomy, the results are somewhat meager. Luft and Olivecrona (1) performed serial sections of the pituitary fossa in one of their cases, in order to determine the presence or absence of glandular remnants. In one patient who underwent hypophysectomy and before that, treatment with radio-active phosphorus, they made biopsies at intervals of two to three months and report striking changes in the histological appearance of the tumor, without describing details. They reproduce two pictures in both of which neoplasm is still recognizable. Picaza, Marinello, Schutte, and Marquez, (2) describe briefly evidence of breast cancer prior to hypophysectomy and show several pictures of histological slides without detailed description, made three, six and twelve months after hypophysectomy. They accompany these pictures with the following statements: tendency to neoplastic cell atrophy, fibrosis (after three months), fewer neoplastic cells, fibrosis continues (after six months), and no neoplastic cells (after twelve months). Most authors (3, 4, 5) discuss the reappearance and gross behavior of metastases. Pearson and his associates (6) make hardly any histological evaluation of their cases. Luft and Olive-

crona (4, 5, 7) discuss the gross findings of their fatal cases, emphasize the importance of the relation between the histological type of the tumor and the success of operation, which is evaluated only by x-ray, calcium deposits, etc. and, make general statements only, such as that favorable results were obtained only with poorly-differentiated cancer as well as with those with a higher degree of differentiation. They emphasize also that this is in contrast to the general opinion that adenocarcinomas should be more sensitive. The same authors mention two factors as being of special importance in judging the results of hypophysectomy: the age of the patient at surgery, and the histological type of the tumor. According to their statistics, scirrhus cancers have the best chance. What we have said does not infer any criticism of these authors, as histological study can be made only in those cases having metastases accessible to biopsy.

Very recently Sloper and Adams (8) wrote an exceedingly interesting paper in which they investigated the influence of hypophysectomy on neurosecretion in four cases of cancer. The survival rate of these cases after operation ranged from 10 to 240 days. The gross findings at the autopsies were given, but no information is rendered about the histological patterns. Luft and Olivecrona (1) emphasize the paramount importance of complete removal of the pituitary in order to avoid merely temporary effect, and report that when the gland has not been removed entirely the downhill course is even accelerated. In order to avoid this, they wash the pituitary fossa with tissue fixation fluid, because, although there may not be a macroscopic remnant, a microscopic residue which has at first no noticeable hormonal activity, may assume this function later. It may also be of interest to quote a paper by Elden and Kumer (9) who performed partial hypophysectomy on a colored female (not for neoplasm) who survived five years. She died of an intercurrent disease, and autopsy revealed macro- and microscopic evidence of marked atrophy of thyroid, adrenals, ovaries and breasts. A moderate degree of virilization was noted. The authors claim that as little as ten per cent of the anterior lobe of the pituitary is sufficient to maintain life. It should be restated here that our case was not a complete hypophysectomy.

In 1953 Pearson, Ray and their associates reported two cases treated by adrenalectomy and castration, followed by hypophysectomy (6). After the latter, a new remission of the tumor was observed. Injection of pituitary growth hormone increased the rate of development of the cancer, measured by calcium excretion. This observation suggests that pituitary hormone or hormones may be an important growth factor for some mammary carcinomas, and supports the statements of Luft and Olivecrona (5) to the effect that the purpose of hypophysectomy in carcinoma of the breast is the elimination of steroid production. Its effect is therefore due not only to indirect bilateral adrenalectomy and indirect castration, but also to the elimination of the hypophyseal growth hormone. Animal experiments and experience in man favor this assumption. According to Harms' treatise (10) on biology of growth, one of the many hormones of the adeno-hypophysis is a true growth hormone. This statement is substantiated in the literature by many experiments in hypophysectomized and nonhypophysectomized animals. That this growth hormone also plays an important role in

regeneration was shown by Schotte (11), Richardson (12), and Zalokar (13) and by many others. It is conceivable that tumor cells are especially susceptible to such growth hormones. An opinion applicable to such an assumption if offered by Cowdry (14) who states that it is possible that hormones other than estrogen and the androgens have an influence on malignant cells and that a sizable proportion of these hormones is of pituitary origin.

These reflections may explain the potential therapeutic value of removing the pituitary. With reference to hormone-dependent tumors such as some cancers of the breast, it is also of interest to note that Korteweg and Thomas (15) found that excision of the pituitary markedly decreased the predisposition to breast cancers. Therefore, the statement of Rawson (16) that his critical survey proved the generalization that "cancerous cells do not respond to hormonal influences" is valid only qualitatively, but not quantitatively. To quote the same author further, different malignant neoplasms are not only sensitive to changes in the hormonal milieu but the potential behavior of such cells, following hormonal therapy, may be predicted in many cases (by calcium elimination, etc.).

Our case, which showed such impressive histological changes following androgen therapy, changes comparable with those observed by Schenken and his associates after administration of estrogen in carcinoma of the prostate (17), enabled us to assume an acute and marked reduction of growth hormone available after incomplete hypophysectomy, and may throw light on the initial effect of hypophysectomy in the case of breast cancer. The assumption of special susceptibility of neoplastic tissue to growth hormone may explain the widespread necrosis after the influx of the hormone has been stopped. How much the associated re-development of immature tumor tissue in association with this necrosis is linked to an increased regenerative power of remainder of the anterior lobe is a matter for speculation, but is somewhat substantiated by animal experiments. All these reflections are based on the fact that our patient did not succumb to the consequences of hypophysectomy, but died of a pulmonary embolism.

It was stated in our case report that sex chromatin was found in all skin biopsies, the adrenal cortex and in some of the tumor cells. In the selection of our material we followed the advice of Lennox (18) and chose especially thick skin slides, examined the nuclei below the stratum germinativum of the epidermis and screened about 150 cells each time. We also found this advice valuable in searching the adrenal cortex for sex chromatin. Our interest in this matter was aroused by two papers by Sohval, Gaines and Gabrilove (19, 20) who initially were not able to identify sex chromatin in cancers of the breast (most probably by chance), but found it in other neoplasms, inflammatory granulomas, epithelial hyperplasia and squamous cell metaplasia. Later they proved that studies of nuclear morphology in individuals with marked aberrations of sex hormonal status indicate the stability of the sex chromatin in this respect. This observation favors the hypothesis that the sex chromatin is by no means an index of hormonal function but derives from portions of the two chromosomes of females. This assumption is strongly supported by our findings that sex chromatin was not

only present in a cancer of the breast, in a state of cancer plus hormonal disturbance (virilization following androgen therapy), but also was found following hypophysectomy (elimination of growth hormone).

SUMMARY

A case of a 62 year old female suffering from extensive cancer of the breast, is reported, in which histological studies were made before and after androgen therapy and hypophysectomy. These three different phases were characterized by poorly-differentiated medullary carcinoma, by a scirrhus-like pattern and by extensive necrosis respectively. It is suggested that more detailed histological examinations should be made in such cases, in order to study the effect of the absence or presence of growth hormone on neoplastic cells (including histochemistry). In all phases sex chromatin was found in skin, adrenal cortex, and tumor tissue, rendering support to the assumption that the presence of sex chromatin has no connection with hormonal function.

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THE RETICULIN RIDDLE

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In 1862, Edward Parrish, about to be elected to the Chair of Materia Medica in the Philadelphia College of Pharmacy and a future president of Swarthmore College, published "The Phantom Bouquet: a popular treatise on the art of Skeletonizing leaves and seed vessels and adapting them to embellish the Home of Taste". His intention was to inform the ladies of Philadelphia how they might have on "their pier-tables and etagières a 'Phantom Case' garnished with airy forms and the well chosen motto 'Beautiful in Death' ", which it seemed was all the rage in the Quaker City in the early years of the War Between The States. Parrish did not claim to have invented the method of maceration which was used to create these elegant parlour ornaments; he pointed out that it was first described by Marcus Aurelius Severinus in 1645 in his *Zootomia Democritaea*, one of the earliest books on comparative anatomy. Severinus was a brilliant neapolitan surgeon, who used refrigeration anaesthesia, but is chiefly remembered to-day for his 'De recondite Abscessuum Natura' (1632), the first text book on surgical pathology.

Severinus kept his method of displaying the fibre skeleton secret, but it was revealed by Frederick Ruysch in the next century, whose works of macabre wit were purchased by Peter the Great in 1717 for \$75,000, and are believed still to be in existence in Leningrad.

It may well be asked what all this has to do with reticulin, but these *momento mori* reveal the ubiquity and relative immutability of this form of connective tissue; when all the cellular tissue has been removed from an organ it is the reticulin network which maintains its character and indeed it is these structural skeletons which are all that remain in an Egyptian mummy and by their abnormalities enable us to deduce the disease processes that were rife three thousand years ago.

Three years after Edward Parrish had enlightened his fair admirers in the art of skeletonizing, Wilhem His, Professor of Anatomy at Basel, wrote his monograph 'Die Haute und Höhlen des Körpers' which was a classification of the tissues of the body on embryological lines. In this treatise he recognized that there was a membrane which separated epithelium from connective tissue—*membrana propria*—which he regarded as a condensation of a closely felted network of fibrils. Others began to recognize this network of fibres in lymph nodes and spleen, but its nature was uncertain. Billroth believed it was a network of branching connective tissue cells (the reticular cells) but Ranvier and Bizzozero in 1872 showed that Billroth's multipolar cells lay on an anastomosing network of fibres, but did not form it. Kupffer (2), using the gold impregnation method

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which revealed the littoral cells which bear his name, saw them in the liver in 1876 but thought they were elastic fibres and his pupil, Oppel (3), publicized Kupffer's name of Gitterfasern (lattice fibres) for the network. However, it was one of Wilhelm His's most distinguished pupils, Franklin P. Mall who clarified the matter. Mall, who came from Iowa, was working with His and Carl Ludwig in Leipzig when Welch was there and became Welch's first fellow in Pathology at The Johns Hopkins Hospital. Mall's first paper (4) emphasized the differences between reticular tissue and elastica and suggested that an elastic fibril is a reticular fibre filled with a tenacious highly refractile substance, viz, elastica. However, his later work (5, 6) is numbered among the great classics of connective tissue research. Mall turned the maceration methods of the skeletonizers into a differential histochemical extraction technique. He applied acids, alkalis, enzymes and bacterial filtrates to various types of connective tissue and showed that by these methods it was possible to distinguish, elastic tissue, white fibrous tissue (collagen) and reticulum. Gelatin could not be obtained from reticulum although he admitted that it was difficult to obtain a tissue rich in reticulum which was relatively free from white fibrous tissue. Mall then showed that the reticulum formed the framework of most of the parenchymatous organs and he tried to trace the development of the three forms of fibre. Oppel (3) in 1891, showed that reticulum fibres could be impregnated with silver using Golgi's method and Siegfried (7) confirmed Mall's finding and believed that he had obtained reticulum fibres in a pure form which he called reticulin. The question as to whether or not reticulin was distinct from collagen seemed finally settled in 1905 when Maresch (8) showed that by the use of Bielschowsky's silver impregnation method, reticulin appeared black while collagen was brown in colour.

So it remained for nearly a quarter of a century, although the idea had been growing that reticulin was a precursor of collagen, with a revival of interest in the cytogenesis of these fibres [Corner (9); Maximon (10)]. Then in 1927, Mallory and Parker (11) reopened the question on the basis of staining reactions and concluded 'Reticulin as a chemically distinct intercellular substance does not exist; it is collagen in separated form rendered prominent by the silver stain'.

In 1928 Foot (12) who had been interested in reticulin for a considerable time, immediately took issue with Mallory and Parker and supported his views by a most detailed histological and biochemical study; he concluded that collagen and reticulin are chemically different but related substances and that reticulin, on hydrolysis, changes into collagen and is probably a collagen precursor.

Two years later Nageotte and Guyon (13) published a reply to Foot, which heralds the present day work on connective tissue fibres as they showed that it was possible to precipitate collagen fibres from an acetic acid 'solution' of collagen from the tendons of a rat's tail (collagène A) and that these reprecipitated fibres had the morphological characters of collagen; fibrous tissue from different sites in various species had varying solubility, and accordingly, they felt that the fact that gelatin could not be obtained from reticulin was not a valid argument for distinguishing the two types of fibres, and that the argyrophilia was determined by the size of the fibres rather than their character.

Nageotte's discovery (1927) of the precipitation of collagen fibres from acetic

acid suspensions (14) stimulated a new field of research. Wyckoff and Corey (15) showed in 1936 that the artificial fibres had the same x-ray diffraction pattern as native collagen fibres and six years later Schmitt, Hall and Jacus (16), in the first paper on the electron microscopy of collagen, found that the reprecipitated fibres had an identical fine structure. However, these studies resulted in two assumptions which have confused work on reticulin for the next quarter of a century. Because fine branching fibres can be precipitated from solutions of collagen, it has been presumed that these fibres are identical with native reticulin and the fact that these fibres, formed *in vitro*, reduce silver solutions so that they appear black, is regarded as a confirmation of this. Although the term reticulin was introduced in 1892 by Siegfried (7) for a substance which he believed was a 'pure' preparation of reticular fibres on an analogy with collagen and elastin, yet at that time and to-day the characters by which reticulin fibres can be identified are the morphological characters of the biological fibre. It remains to be shown that biological fibres of this type wherever they may be found in animals of all species are identical in ultrastructure and chemically; this requires the ability to isolate the biological fibres without denaturation and then submit them to chemical and physical analysis.

This semantic confusion also exists in the use of the word elastin and to a lesser extent with collagen, where it is beginning to be recognized that collagen is more correctly used as a collective term for a range of biological fibres, which though they may appear similar by staining characters under the light microscope, and within the limits of chemical analysis are comparable, yet vary considerably both in their physiological and physical characters.

It is also erroneous to pay undue attention to the staining reactions of fibres with ammoniacal silver solutions under abnormal conditions. With tissue sections, using the modification of the Maresch-Beilschowsky method with which one is familiar, it is possible to obtain, under controlled conditions, consistent results and under these conditions, the argyrophilia is a reliable histological indication of reticulin. However, by modifying the conditions it is easy to ensure that either every type of fibre or no fibres will stain black with silver; accordingly, it is quite unjustifiable to assume that artificial fibres obtained by precipitation on one matrix or another which stain black with silver are reticulin, nor can it be assumed that chemical treatment of collagen or reticulin fibres which modify their reaction with ammoniacal silver solutions is of itself an indication that collagen and reticulin are identical. It is deductions of this type which must invalidate the conclusions which Irving and Tomlin (17) draw in 1954 from their carefully controlled experiments on the argyrophilic properties of collagen and reticulin.

In 1942, the year in which the first electron micrographs of collagen appeared, Heringa and Weidenger (18) published the results of an investigation of collagen and reticulin using histological, chemical and x-ray diffraction methods, which they believed showed fundamental differences between these two fibres. They compared a reasonably pure sample of collagen from rat tail tendon, with 'reticulin' obtained from human spleen by tryptic digestion followed by boiling; they also examined the dermis of young rats which provided a mixture of col-

lagen and 'reticulin'. This chemical analysis revealed that 'reticulin' had a higher sulphur content than collagen and a lower waterbinding capacity, while the x-ray diffraction pattern of 'reticulin' yielded an amorphous pattern. They concluded that reticulin had stronger intermolecular bonds than collagen and the molecular chains were in a highly coiled state, in fact they suggested that reticulin could be regarded as a sort of vulcanized collagen. Although this work was accepted as resolving the problem at the time, in recent years the purity of their reticulin sample has been questioned and Irving and Tomlin (17), having prepared material in the same way as the Dutch workers, showed that their 'reticulin' contained large amounts of thermally shrunken collagen and no attempt had been made to remove the carbohydrates of the ground substance.

During their studies of gas gangrene, Macfarlane and McLennan (19) discovered in 1945 that part of the exotoxins of the clostridium was a proteolytic enzyme which attacked white fibrous tissue which they called 'collagenase'. It is almost certain that Mall unknowingly took advantage of the activity of this enzyme in his studies in 1890, and in 1945 when I was investigating the specificity of this enzyme, I was able to show that both reticulin and collagen were attacked and came to the conclusion that the two fibres forms were probably chemically identical, but differed in the degree of molecular condensation (20). In retrospect it is clear that such an assumption was unjustified, although there is no question but that this group of clostridial proteolytic enzymes are remarkably specific in their substrates, which are limited to the collagen family of scleroproteins, indicating the hydrolysis of a peptide bond peculiar to the proteins.

During a study of the action of clostridial collagenase on various tissues, I discovered that fine fibres exist which morphologically and by staining reactions would be classed as reticulin, yet by enzymic analysis must be excluded from the collagen family (21, 22). For example, in the stroma of the ovary there are fine branching argyrophilic fibres which are destroyed by trypsin but are collagenase-resistant and Bembridge et al. (23) in 1952 described branching fibres in the ciliary region of the vitreous which have identical enzymic reactions. These observations emphasize that morphology and staining reactions with the light microscope are not sufficiently specific criteria for the identification of reticulin.

In 1946 the periodic acid schiff reaction was introduced as a histochemical method by McManus (24) and at once was applied to the study of connective tissue.

It soon became apparent that reticulin fibres and basement membranes that were argyrophilic all gave a positive reaction with the P.A.S. reagent, but curiously enough it was not emphasized, until I mentioned it in 1952, that collagen gave a negative reaction (21), although Lillie (25) was not entirely in agreement and in 1953 still maintained that collagen gave a positive P.A.S. reaction (26).

There is still uncertainty about the substances in connective tissue which are revealed by the P.A.S. reaction, but the majority would agree with Glegg, Eidinger and Leblond (27) that it stains protein bound neutral sugars. This

histochemical difference between native reticulin and collagen was confirmed when Kramer and Windrum (28) with their sulphation metachromasia reaction showed that reticulin was metachromatic and collagen orthochromatic.

An aminoacid analysis of reticulin was attempted by Bowes and Kenten (29) using adipose tissue and lymph nodes. They found that the aminoacid distribution of reticulin was similar to that of collagen except for a lower proline and hydroxyproline content; their samples must have been contaminated with collagen, as no attempt was made to remove the fibrous strands in the fat or the capsules of the lymph nodes.

Gross (30) described the electron microscopic and x-ray diffraction characters of the dermis of young rats, having found that in the newborn animals almost all the fibres were argyrophil, but as they aged an increasing proportion of the fibres developed the staining reactions of collagen. The electron micrographs showed that in all ages the fibrils showed cross striations with an average period of 640 Å characteristic of collagen, but the average width of the fibres increased with age; in the newborn the fibres were mostly about 600 Å wide, but by three months the average width was more than double this. The x-ray diffraction pattern of the dermic fibres whether from the newborn or the adult rat, was also typical of collagen, but in the immature animals a diffuse halo was superimposed, which could be removed by trypsin, and which Gross attributed to the large amounts of ground substance which was present in the newborn animals.

It is apparent that all the investigations of reticulin over the last sixty years have been bedevilled by the difficulty of finding material for examination which was acceptable reticulin histologically, unmixed with collagen and unaltered by chemical extraction methods.

This was the problem which we started to attack seven years ago and though our progress has been slow, yet I believe it has resolved some of the points which have been in doubt for so long and has opened the way to investigations of the physiological and pathological importance of reticulin; its morphological significance has long been appreciated.

It was first necessary to find a tissue rich in reticulin and poor in collagen, and after a survey of a wide range of organs, we selected the subcortical tissue of the kidney, as its fibrillary portion consisted almost exclusively of basement membrane reticulin and it was comparatively easy to dissect out the small amount of collagen around the blood vessels. Kramer and Little (31) made an electron microscopic study of this material and showed that it consisted of a feltwork of fine (down to 100 Å in diameter) interlacing fibrils having the 640 Å periodicity of collagen embedded in an electron optically homogeneous ground substance. A similar structure was found in samples of reticulin from spleen, lymph nodes, heart muscle, liver and adrenal, though in these organs there was contamination with histological collagen; more recent work on sectioned material has confirmed these findings.

Weiss (32) has made a most fascinating study of the epithelial basement membrane of larval amphibians, showing that it is a lamellar structure of twenty plies, each ply consisting of parallel arranged collagen fibrils of uniform diameter, in register, and that the fibril direction of each ply is at right angles to the next

one; the fibrils are embedded in a matrix of homogeneous ground substance and the thickness of each ply is uniform, averaging about 2,000 Å. During regeneration of the membrane, the fibrils, which are derived from the connective tissue cells in some precursor state, are shed into the matrix where they assume their filamentous forms. At first the filaments are in random disarray and it would seem that the orientation and stratification of the fibrils appears first at the epidermal side of the membrane; what it is that determines the ordering process is as yet unknown nor can we be sure that mammalian reticulin basement membrane has a similar pattern of fabric, but it is certain that Weiss' work has illuminated in a masterly fashion some of the problems of biomolecular organization.

Returning to our own work, in 1954 Little and Windrum (33) found that the x-ray diffraction of renal basement membrane reticulin gave a pattern characteristic of collagen but in addition to the collagen bands, other rings were seen at 2.5, 2.35 and 2.2 Å. The next step was a chemical analysis of this material which was carried out by Windrum, Kent and Eastoe (34) in 1955. It should be emphasized that in each stage of our investigation the material was controlled histologically and the samples submitted to the electron microscope, x-ray camera or clinical analysis were cell free fibrillary material, having the morphological characters, under the light microscope, of reticulin, staining black with silver, giving a positive P.A.S. reaction and becoming metachromatic after sulphation. This material is little affected by boiling water, [Dresner and Schubert (35) using similar material only obtained 25 per cent gelatine in contrast to 98 per cent from tendon collagen], dissolves very slowly on heating with strong hydrochloric acid, leaving a large quantity of brown residue, but is readily soluble in boiling normal sodium hydroxide. The detailed chemical analysis showed it to consist of 85 per cent protein and its aminoacid composition is very similar to that of collagen. Carbohydrate is present to the extent of 4.2 per cent non-hexosamine, the sugars identified being galactose, mannose and fucose, together with a small amount of glucosamine; no uronic acid or sulphate ester was detected. In addition, it contained 10.9 per cent bound fatty acid of which about 95 per cent was myristic acid, the rest palmitic. Thus, renal basement membrane reticulin is a lipo-glyco-protein in which the aminoacid constituents are very similar to those in collagen, and although it would be quite unjustified to assume that reticulin from other sources is of identical chemical nature, yet if basement membrane reticulin is generally of this nature it would conform well with its known character; perhaps it should be mentioned that although some carbohydrate may be present in collagen it is of the order of 0.5 per cent (36) and this may well be a contaminant as the analysis was carried out with commercial hide powder, which probably contains some reticulin and elastin.

Now that we had shown that reticulin, although a member of the collagen family was distinct both chemically and structurally from the collagen of fibrous tissue, it seemed desirable to try and determine what relationship, if any, basement membrane reticulin had to the various soluble collagens that have been described. Accordingly, the renal tissue was treated with phosphate and citrate buffers, weak acetic acid, and weak alkali, using the same techniques as are

employed for the extraction of the various soluble collagens and then the tissues were examined histologically; it was found that following exposure of the tissue to the buffers, etc., no functional or structural alteration of the basement membrane reticulin could be observed with the light microscope although there were striking alterations in the collagen and ground substance; it seems probable that 'Collastromine' described by Tustanovskii et al (37) as the insoluble stable component of collagen was, in reality, reticulin basement membrane (38). When the extraction technique was applied to granulation tissue from a healing wound, it was found that although the basement membrane reticulin was unaffected, the fine, wavy, non-branching argyrophil fibres which are always to be found in areas of cellular fibrillogenesis, were dissolved, like the mature collagen fibres, and ceased to be argyrophilic. Jackson and Williams (39) have confirmed these findings during a study of the carrageenin granuloma; extraction with sodium chloride, which removes 'neutral salt soluble collagen' caused the disappearance of argyrophil fibres, while treatment with citrate buffer, which extracts 'citrate soluble collagen' removed the fibres almost completely.

We can now see that much of the dispute and confusion that has existed with regard to reticulin over the last thirty years has been due in large part to the various authors arguing about different tissue elements and failing to recognize that there are several sorts of fine argyrophilic fibres in connective tissue.

Accordingly, it might be useful to set out a brief summary of the various fibres that have been called 'reticulin'.

Al. these fibres are fine (of the order of $1\ \mu$ diameter as seen in the light microscope) isotropic and branching. They stain faintly with acid fuchsin (van Gieson's stain), accept the acid aniline dyes in the Mallory or Masson Trichrome method, and appear black in both toned and untuned preparations impregnated with silver by the Maresch-Bielschowsky method or its modifications.

A. *Collagenous reticulins*. Scleroprotein fibres having the aminoacid composition of collagen and the ultrastructure of collagen as revealed by electron microscopy; they resist tryptic digestions but undergo dissolution when incubated with clostridial collagenases.

(a) *Natural fibres found in the tissues of various animal species, giving a positive reaction with the periodic acid schiff reaction and becoming metachromatic after sulphation.*

(1) *Basement membrane reticulin*. This is the classical reticulin originally described by Mall, etc., lying between epithelium or endothelium and connective tissue and forming the fibrillary matrix of lymphoreticular tissue. It is extremely stable and in human kidney is a glyco-lipo protein. It is not a precursor of mature collagen.

It must be mentioned that not all basement fibre membranes are of this type; the notable exception being the basement membrane of the renal glomerulus. This is normally non-argyrophilic although it is P.A.S. positive and becomes metachromatic after sulphation. It has distinct staining reactions (40, 41) while electron microscopic studies (42) has failed to reveal the presence of collagen-type fibrils.

This is of some importance as Cruickshank and Hill (43), using the fluorescent antibody technique of Coons and Kaplan (44), showed that antiglomerulus serum 'stained' both renal glomerular basement membrane and basement membrane reticulin, but not collagen fibres. They quite rightly stated that their experiments indicated a common antigen in these two tissue elements but this work has been misinterpreted as a specific method for identifying reticulin.

(2) *Immature argyrophilic collagen fibres.* These are found in embryonic and regenerating areas of connective tissue formation and were the type of fibre studied by Gross (30) with the electron microscope. They are fine wavy fibres which though they do branch, do not show the angular branching of basement membrane reticulin; they merge very closely with the developing collagen fibres and indeed appear to be incorporated and replaced by the collagen fibres. They are readily soluble in sodium chloride and citrate buffer and although it cannot yet be said that they are identical with any of the soluble collagens, it is clear that they have close affinities with 'neutral salt soluble collagen' (45, 46).

(b) *Artificial fibres.* These are the precipitated fibres prepared from various types of soluble collagen extending back to the collagen A of Nageotte (14), 'procollagen' citrate, soluble collagen, etc. According to the method of preparation they may or may not be argyrophilic.

B. *Non-Collagenous Reticulins.* Little is known of these fibres; they are argyrophilic, soluble in trypsin and collagenase resistant. They have been described in the ovarian stroma and vitreous.

Klemperer has frequently emphasized that our understanding of disease processes must be grounded on a clear understanding of their morphological lesions and only from there can we extend into the fields of pathogenesis and aetiology; his own contributions have fully substantiated this viewpoint.

Accordingly, it might be legitimate to discuss the possible significance of the reticulin basement membrane in disease, in the light of the work which has been reviewed here.

The mechanical importance of this closely meshed membraneous network of considerable stability is at once apparent, and the liver can be selected as an example. There are many types of acute hepatitis in which there is focal dissolution of liver cells. During regeneration, provided the basement membrane has not been destroyed, the normal architecture will be maintained and afterwards the liver will be restored to normality both functionally and anatomically. On the other hand, if the noxa has been more severe and there has been destruction of basement membrane as well as hepatic cells, the regeneration will be irregular, with scarring of the stroma, disturbance of blood supply and a cirrhosis will result.

In neoplastic growth one of the many problems to be resolved is the physico-chemical changes that enable the neoplastic cells to break through the basement membrane and into the surrounding tissues; it is an aspect of histology which is

the daily concern of the surgical pathologist assessing the significance of tissue changes and sometimes it is possible, by studying the basement membrane pattern of a piece of necrotic material, to determine its nature and significance.

These and many other examples are familiar enough and though it may be that the value in diagnostic pathology of studying alterations in the basement membrane has not always been stressed sufficiently, I would prefer to leave this on one side and consider the possible significance of the chemical nature of reticulin basement membrane, if it is justifiable to assume that our findings with regard to the kidneys are applicable to other tissues.

In many 'degenerative diseases' we have striking alterations in the basement membrane which is thickened, altered, so that it becomes 'hyalined' and free fat can be detected in it. It has been assumed that this fat is derived either from the blood stream or from cellular breakdown, but if we accept that there is 10 per cent of fatty acids in basement membrane, it would not be unreasonable to consider this as a possible source and to study the factors that encourage the breakdown of the stable membrane. In amyloidosis, in the first instance, the abnormal protein is absorbed on to the reticulin basement membrane and the question of its metabolic activity is at once of importance. Lastly, we must recognize that almost all metabolic exchange between the circulation and the cells must take place through this membrane and so its variations in permeability in health and disease are of paramount importance. It would be possible to generalise in this manner for a considerable time, but it would not be very profitable, as this particular aspect of connective tissue has been comparatively neglected. Now that the nature of reticulin is beginning to become apparent, its functional significance can be investigated.

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LYMPHOID NODULES IN THE HUMAN CERVIX

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Within the past year examination of a cervix revealed multiple lymphoid nodules. Inquiry amongst pathologists and gynecologists interested and experienced in gynecological pathology indicated that this was a rare finding. It was accordingly thought worthwhile to study the material available to us to determine the frequency of this condition and if possible its significance.

MATERIAL

The material reviewed consisted of 286 biopsies of the cervix and of sections of complete cervixes from 229 hysterectomy specimens. In 47 of the latter, multiple sections from as many as eight quadrants of a cervix were studied. The endometria from the majority of uteri were also available for examination. The tissues were routinely stained with hematoxylin and eosin. In selected cases the Wilder reticulum stain, Masson stain and the periodic-acid Schiff method were also employed.

RESULTS

In ten cervixes discrete accumulations of lymphoid tissue occurred. These had the architecture of lymphoid nodules and varied in number from one to six in a single section. These structures were found superficially in the stroma just beneath the surface epithelium, and deeper in the fibromuscular coat. Most of the cervixes showed varying degrees of banal inflammatory cell infiltration apart from these lymphoid nodules. However, there appeared to be no direct relationship. Severe degrees of non-specific chronic cervicitis were commonly encountered without follicle formation.

In twenty-nine cases, focal accumulations of lymphocytes were encountered which were not interpreted as lymphoid nodules. These were not sharply demarcated from adjacent inflammatory reaction and more particularly did not have the architecture of lymphoid follicles.

CASE REPORTS

Case No. 1.

A 56 year old, white multipara, was admitted because of profuse, yellowish vaginal discharge and post menopausal staining for one month. Pelvic examination showed the cervix to be enlarged and softened. The external os was stenosed

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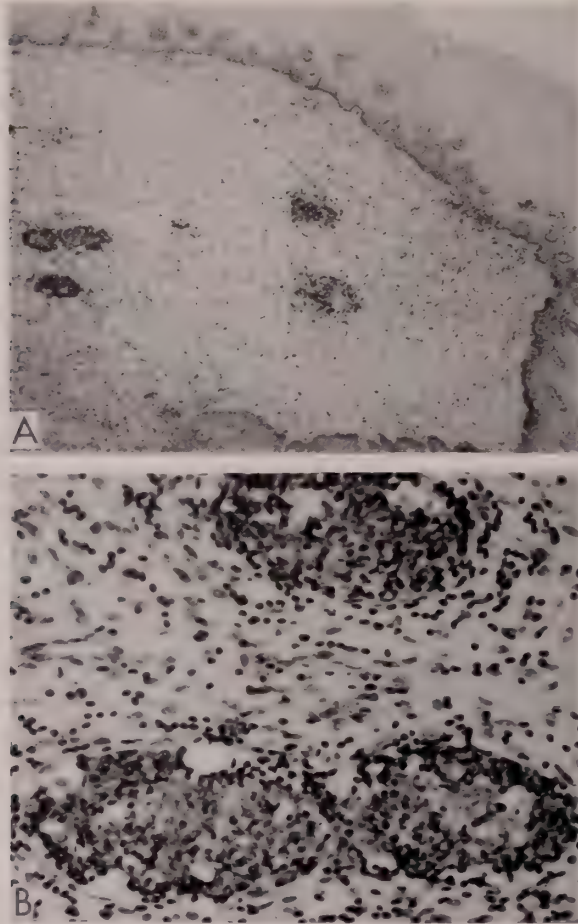


FIG. 1, Case No. 1. (A) The edematous fibromuscular portion of the portio-vaginalis shows slight inflammatory cell infiltration and four lymphoid nodules (H. and E. $\times 50$). (B) Three lymphoid nodules showing central reticular cells and concentration of lymphocytes peripherally (H. and E., $\times 300$).

and through it a thick, yellowish discharge exuded. A diagnosis of pyometra was made and curettage and biopsy were performed.

The specimen obtained from the cervix consisted of a wedge of tissue covered by stratified squamous epithelium. The fibromuscular coat of the portio-vaginalis was edematous and showed a loose, diffuse infiltration with lymphocytes, plasma cells and occasionally polymorphonuclear leucocytes. In addition, there were six discrete lymphoid nodules. These were composed of central conglomerates of reticular cells with a marginal collar of lymphocytes (Fig. 1). Lymphocytes were also sparsely present and intermingled with the larger central cells.

Three months later repeat biopsy of the cervix revealed persistence of the chronic, diffuse inflammatory process previously seen. In one area there was a perivascular conglomeration of lymphocytes together with large stellate reticular cells. These were associated with a few thin-walled capillaries.

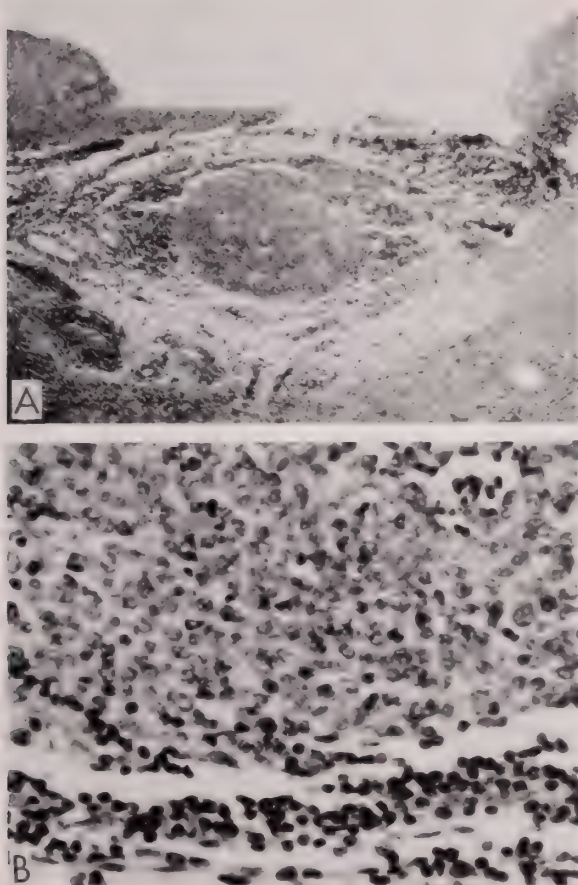


FIG. 2, Case No. 2. (A) A discrete lymphoid nodule with a large germinal center. There is surrounding edema and infiltration with inflammatory cells (H. and E., $\times 80$). (B) Portion of a germinal center with marginal small lymphocytes and phagocytosis of nuclear debris (H. and E., $\times 500$).

Case No. 2.

A 37 year old multiparous Negress had a total abdominal hysterectomy for myomata of the uterus.

On microscopic examination of the cervix a large, well-delineated lymphoid nodule was noted in the stroma just beneath the squamocolumnar junction (Fig. 2). The center of the follicle was composed almost entirely of reticular cells surrounded by a marginal zone of small lymphocytes. Moderate phagocytosis of nuclear debris was also noted in the center of the follicle. The adjacent stroma was edematous and loosely infiltrated with a variety of mononuclear inflammatory cells. The endocervix otherwise was devoid of inflammatory infiltration. In the ectocervix there was slight infiltration with small lymphocytes with a tendency towards perivascular condensation. In that portion of the fibromuscular coat of

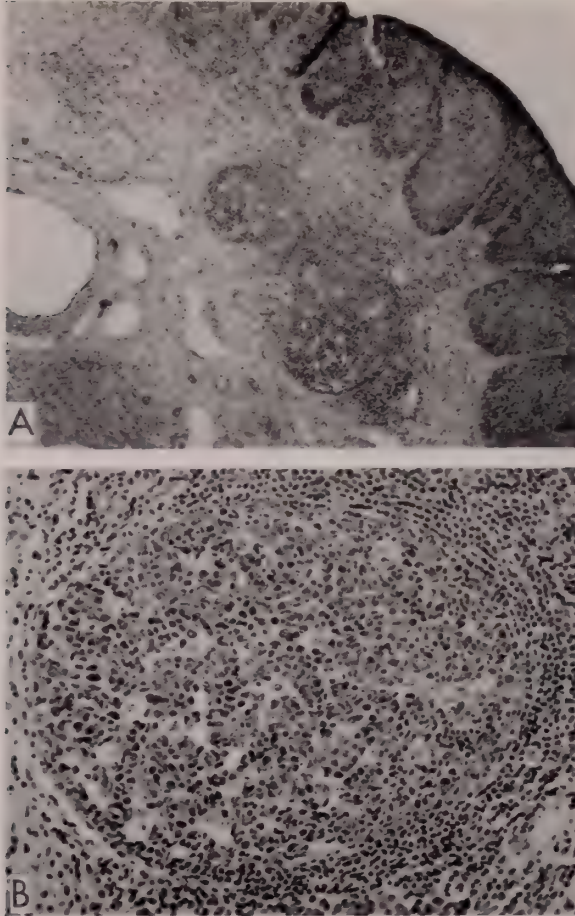


FIG. 3, Case No. 3. (A) Intraepithelial carcinoma of the cervix with lymphocytic infiltration of stroma. Two discrete lymphoid nodules are present (H. and E., $\times 46$). (B) Higher magnification of the larger nodule (H. and E. $\times 250$).

the cervix nearest to the lower uterine segment there were two smaller loosely arranged nodules composed largely of reticular cells and fibers.

*Case No. 3.**

Clinical data for this case was not available. A section of the cervix revealed carcinoma in situ. In the underlying stroma there were two discrete lymphoid nodules with prominent germinal centers. In the adjacent stroma a more diffuse mononuclear inflammatory cell infiltration was noted (Fig. 3).

Case No. 4.

A 44 year old white female had had a subtotal hysterectomy and bilateral salpingo-oophorectomy. She was admitted for prolapse of a cervical stump for

* From the Armed Forces Institute of Pathology, Washington, D. C., courtesy of Captain W. M. Silliphant, (MC), USN, The Director.

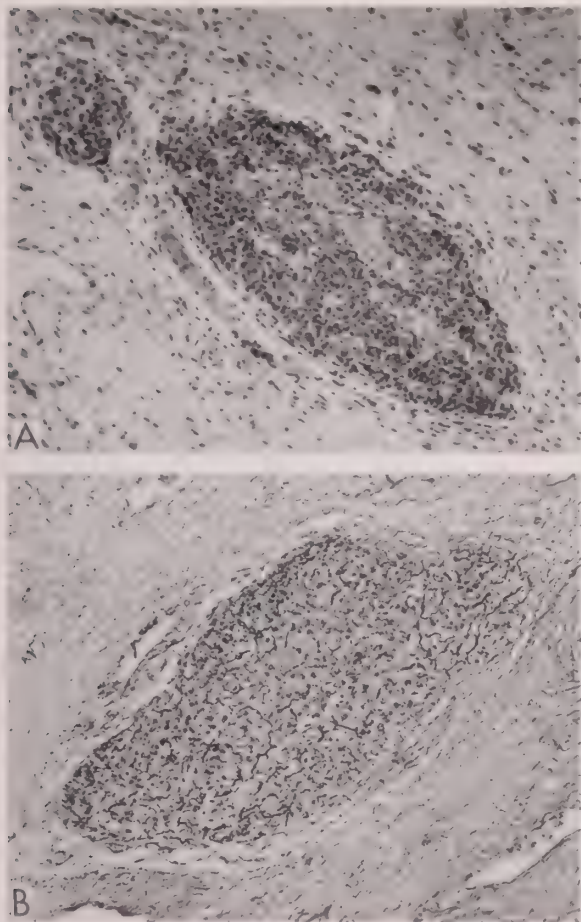


FIG. 4. Case No. 4. (A) Lymphoid nodule deep in the fibromuscular coat of the cervix (H. and E., $\times 200$). (B) Wilder impregnation demonstrating argentophilic fibrillar stroma ($\times 200$).

which she had been wearing a pessary. Operation included plastic repair and biopsy of the cervix.

Two pieces of tissue from the cervix were examined. The stroma of the endocervix was edematous and superficially contained a sparse scattering of inflammatory cells, most of which were lymphocytes and plasma cells. In one piece of tissue there were two discrete lymphoid nodules in the fibromuscular coat. These were composed centrally of large pale cells interspersed with lymphocytes which were more prominent at the periphery (Fig. 4A). In silver stains, a prominent meshwork of reticulum fibrils was evident (Fig. 4B). A third, smaller, poorly defined nodule was noted beneath the endocervical epithelium just about at the squamo-columnar junction.

Case No. 5.

A 40 year old white female had a total hysterectomy for myomata.

In a section of the cervix lymphocytes and plasma cells together with mild

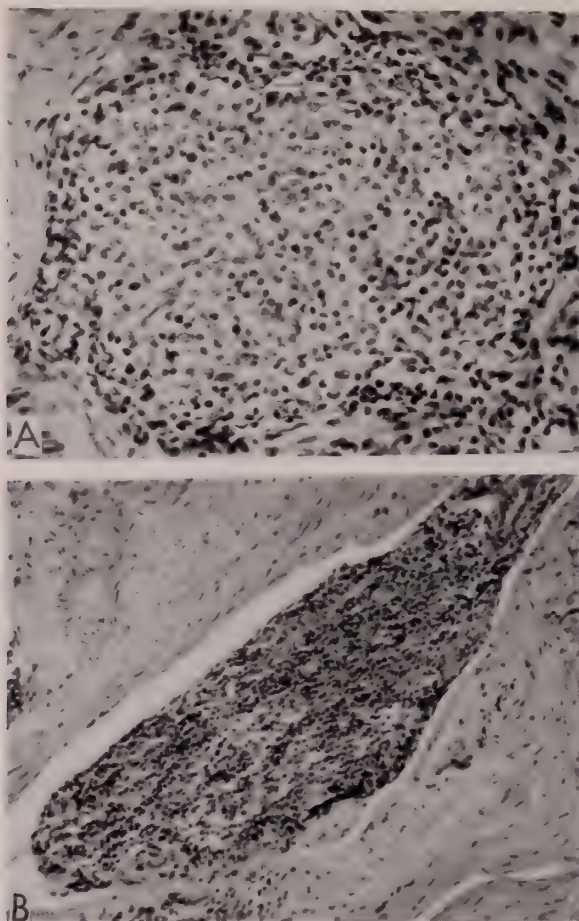


FIG. 5.(A) Case No. 5. Follicle with prominent germinal center in fibromuscular coat (H. and E., $\times 300$). (B) Case No. 10. Lymphoid nodule in wall of lymphatic channel (H. and E., $\times 200$).

hyperemia were noted surrounding glands at the squamo-columnar junction. Deeper in the fibromuscular coat there was a discrete lymphoid nodule composed of scattered lymphocytes in a meshwork of large pale reticular cells and fibrils (Fig. 5A).

Case No. 6.

A 44 year old white multipara, was admitted for menometrorrhagia. A hystero-gram revealed a submucus myoma. Biopsies were obtained from four quadrants of the cervix. They showed varying degrees of diffuse inflammatory cellular infiltration in the underlying stroma. This ranged from a sparse exudation of lymphocytes, plasma cells and polymorphonuclear leucocytes to somewhat denser infiltrates of similar cells with some tendency to periglandular localization. In the midst of the more diffuse inflammatory process there was a focal compact conglomeration of large pale reticular cells.

Case No. 7.

A 42 year old white multipara had a total hysterectomy for multiple myomata.

This case was studied by eight step sections comprising the entire cervix. In one area only was a lymphoid nodule noted. This was in a section which showed the superficial stroma of the endocervix to be edematous. There was a sparse, loose scattering of plasma cells just beneath the squamo-columnar junction. Here there was a single, sharply circumscribed lymphoid nodule.

Case No. 8.

A 50 year old Negress whose previous history included four abortions had a total hysterectomy and bilateral salpingo-oophorectomy for multiple myomata and chronic salpingitis.

The cervix showed edema and mild inflammatory cell infiltration in the superficial stroma. Scattered at random beneath the endocervical epithelium were four sharply circumscribed follicular aggregates of lymphocytes and reticular cells supported in a loose fibrillar stroma.

Case No. 9.

A 26 year old white multipara had had incisions of the cervix and insertion of a drain, presumably for cervical abscess. She continued to have vaginal discharge and staining. Pelvic examination revealed an hypertrophied cervix with a fistula in the anterior lip. This was repaired and a biopsy done.

Microscopic examination of cervical tissue showed moderate, chronic, non-specific inflammatory change and a single, well defined lymphoid nodule in the vicinity of the squamo-columnar junction. This structure consisted of small lymphocytes enmeshed in reticular cells. Cells at the periphery revealed degenerative changes.

Case No. 10.

A 53 year old white multipara had had a subtotal hysterectomy and bilateral salpingo-oophorectomy eight years previously for pelvic endometriosis. Pinkish vaginal discharge was noted. Pelvic examination showed punctate reddening and atrophic changes of the mucosa of the cervix and vagina.

A biopsy of the cervix revealed marked infiltration with mononuclear inflammatory cells. There was a focus of superficial necrosis in the endocervix. Slitlike endothelial lined channels, which appeared to be lymphatic vessels, were prominent throughout the fibromuscular stroma. In the walls of these vessels, there were focal accumulations of lymphoid tissue in nodular configuration. These totaled six in number and consisted predominantly of small lymphocytes intermingled with varying numbers of large pale reticular cells and argentophilic fibrils (Fig. 5B).

COMMENT

We have been unable to find a systematic study or description of lymphoid nodules in the human cervix. In the textbook of histology by Maximow and

Bloom (1) there is an illustration of a sagittal section of a presumably normal cervix in which a lymph follicle is clearly depicted in the stroma of the mucosa near the squamo-columnar junction. A lymphoid follicle in a case of cervicitis is depicted also in a recent paper by Foraker (2).

This study indicates that lymphoid nodules are uncommon in the cervix and when present are usually associated with chronic inflammation. However, it is clear that their incidence is greater than is generally known. Thus we have noted lymphoid nodules in 10 of 468 cervixes. In three cases these structures were found in only one of multiple sections from varying quadrants of the cervix. Our incidence of the occurrence of lymphoid nodules in all likelihood would have been higher had all of the cervixes been studied by multiple sections.

Lymphoid nodules may be single or multiple, are generally associated with chronic inflammation and are most commonly found near the squamo-columnar junction. The lymphoid nodules which we have found varied in structure, some being composed predominantly of small lymphocytes (Figs. 4A, 5B). Others revealed germinal centers in different stages of development (Figs. 2, 3, 5A). This variability of structure is well known as is the potential for the development of lymphoid nodules in any loose adult connective tissue in response to a variety of injurious stimuli.

The patients ranged in age from 26 to 56 years and included menstruating, menopausal and post menopausal women. Inquiry into their general status disclosed no co-existing factors which might result in systemic stimulation of lymphoid tissue. Blood cell counts and differentials were within normal range. In four patients local factors of probable significance were encountered. These included the wearing of a pessary, a fistula of the cervix, pyometra and intraepithelial carcinoma of the cervix in one case each. These patients had obvious cause for prolonged chronic irritation of the cervix. Nevertheless, there is little correlation between the severity of chronic non-specific inflammation and the appearance of lymphoid nodules for we have encountered many cases of marked inflammatory infiltration in the cervix without lymphoid nodules.

The occurrence of lymphoid nodules in the cervix could not be related to the presence of lymphoid tissue in the endometrium. In the course of this study aggregates of lymphocytes were found in about fifty percent of the endometria examined. These were generally multiple, located in the zona basalis and did not have the configuration of true lymphoid nodules.

ACKNOWLEDGMENT

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JULIUS SCHOTTLAENDER, PIONEER PATHOLOGIST IN OBSTETRICS AND GYNECOLOGY: WITH PERSONAL RECOLLECTIONS AND NOTES ON EARLY CONTRIBUTIONS TO HISTOPATHOLOGY OF INCIPIENT UTERINE CANCER

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This volume is dedicated to Doctor Paul Klemperer, an outstanding pathologist of the present time and a pioneer in his field. His present interest in the history of pathology affords me the appropriate occasion to outline briefly the life and work of Julius Schottlaender, a pioneer in a branch of pathology represented by very few men at the turn of the century. Schottlaender may be regarded in point of fact as the first pathologist to limit his work to obstetrics and gynecology. His contemporaries in this special field were F. Hitschmann, Oscar Frankl also of Vienna and J. A. Amann of Munich. Robert Meyer of Berlin was several years younger and became prominent shortly after Schottlaender's career ended in 1917. Carl Ruge and C. Gebhard, like R. Meyer, had both practiced general medicine before specializing in gynecological pathology. According to R. Meyer, (1) Gebhard, a student of Ruge for ten years, was the author of the first complete textbook on gynecological pathology (Leipzig, 1899). Walter Schiller, a pupil of Schottlaender, succeeded his chief as head of the II University Frauenklinik Laboratory.

There are few survivors among Schottlaender's pupils; only two are living in this country while of his many pupils and younger associates, none could be found in Vienna last summer who could tell me anything about him in the city where the crowning work of his life was done.

Last June on a visit to Vienna, after a previous one of 1937, I found the Laboratory of the Second Frauenklinik built in 1908 according to my teacher's design in the same condition in all respects except two: The one was that the head of the laboratory was a young man who scarcely knew of his erstwhile predecessor and no one was around in and about that famous laboratory who had ever seen him in person. The second change was the conversion of the animal experimental room into a hormonological laboratory. The present head of this II Frauenklinik, Hans Zacherl, had known of Schottlaender but had never met him and was unfamiliar with any items of biographic or personal interest. This was also the case with Tassilo Antoine, Head of the I University Frauenklinik where Oscar Frankl, Schottlaender's contemporary and colleague was the chief of laboratory under F. Schauta, Director of that Clinic. Herman Knaus now Gynecologist-in-Chief at the Lainz Hospital, Vienna, who knew Schottlaender could add nothing personal but was very helpful in introducing me to Doctor Marlene Jantsch in charge of the Institute for the History of Medicine of the University of Vienna. She very generously placed such material at my disposal which enabled me to get a glimpse of the life story of the master pathologist

under whose guidance and instruction I had the privilege of working for a year (1909-1910).

The following data are largely collated from the necrologies appearing in various medical journals in Austria and Germany. They appeared during the first World War. As Schottlaender's chief work was done in Germany and Austria, mostly in Heidelberg and Vienna, it is reasonable to suppose that his German speaking colleagues would be the most likely to write authoritatively about him. Were it not war-time, other journals outside of Austria and Germany would have taken notice of Schottlaender's death. I have interpolated here and there some personal recollections pertinent to the biographic notes.

Schottlaender's closest and most admired friend and chief, Alphons von Rosthorn, unfortunately had passed away eight years before him in May, 1909. Von Rosthorn probably knew him most intimately and accepted the position of Director of the II Universitat Frauenklinik with the expectation that Schottlaender would head his laboratory. The new II. Universitat Frauenklinik opened up in 1908. The position was created by Rudolf Chrobak for his favored pupil von Rosthorn of whom the old chief was very proud and, it was universally admitted, for just reasons. The same relationship existed between von Rosthorn and Schottlaender. There was a spirit of dedication in this interpersonal relationship between the old and the new chief and the latter's associate, which was exhibited by all three men during the "golden era" of Viennese medicine. It is of passing interest that von Rosthorn also died of a coronary attack like his friend and associate, Schottlaender. Evidently he was stricken while hunting, as he was found dead near his horse. In connection with this fatal incident I recall visiting Professor von Rosthorn a month before to pay him my respects. My eyes caught sight of a plate on his desk stacked with cigarette ashes and stubs and I wondered how long it took to accumulate that heap. As if he guessed my unspoken question, he pointed to the plate and said, "there is part of me and it's only 24 hours". He spoke English fluently.

I should like to record here my indebtedness to my former chief and predecessor Doctor Joseph Brettauer for his great kindness in sending me, after finishing my house surgeonship at The Mount Sinai Hospital, to von Rosthorn—his friend and erstwhile classmate with the request that he turn me over to Schottlaender for training in gynecologic and obstetric pathology. Von Rosthorn sent for Schottlaender and told him I was "his man" and to do what he could "with" me. I appreciated the kindness greatly at the time but scarcely realized how much this gesture would influence my future.

The data of biographic and medical interest in connection with Professor Schottlaender's life and work are here recorded as gleaned chiefly from the eulogies of Ernest Wertheim (2) and of Fritz Kermauner (3), successors in turn of A. von Rosthorn. Some estimates of Schottlaender's personality and work as expressed by the renowned A. Martin (4), J. Halban (5), R. Meyer (6) and G. A. Wagner (7) are also included.

First notice of Schottlaender's death appeared in the *Munchener Medizinische Wochenschrift*, Vol. 64, No. 23, June 5, 1917, although it occurred on May 29,

1917, in Kiel where he was serving as scientific military adviser with the rank of Marineoberstabsarzt. Despite his age which exempted him from military service in the German Army, Schottlaender volunteered for service early after the outbreak of the First World War and was not able on account of his duties to return again to Vienna.

Of German descent, Schottlaender was born in St. Petersburg, Russia on April 12, 1860. He went to Germany as a young boy for his education in Heidelberg and Munich, where he studied medicine, establishing himself in Heidelberg in 1887. He chose the field of gynecology at once. His early teachers were F. A. Kehrler in Heidelberg and A. Martin in Berlin.

He became Dozent in 1893 and Extraordinary Professor in 1897 in Heidelberg. There, von Rosthorn invited him in 1903 to take charge of his newly enlarged pathological laboratory at the same time increasing his teaching activities. His lectures on the normal and pathologic histology of the female generative organs became so popular that as Kermauner remarks, all the younger physicians of the clinic flocked to hear them.

In 1908, von Rosthorn was called to head the II University Frauenklinik of Vienna and he was accompanied by Schottlaender who took charge of the then considered most adequately equipped laboratory in all Austria. Like Kermauner, I may say that in 1909 when I first saw the laboratory, it had all the facilities of a modern laboratory that could be found anywhere, for efficient pathological histological work (Fig. 1). What made a deep impression on me at the time was the fact that it served only one special branch of medicine constituting an integral part of the gynecological-obstetrical service. In this connection it may be recalled that the establishment of a special obstetric gynecological pathological laboratory was not favored by the general pathologists who were reluctant to relinquish valuable material for teaching purposes and for research. It had been obligatory in Vienna to send all specimens to the Institute of General Pathology where they were examined and reported. Gynecologists were permitted on occasion to use some of the pathological material for special study and publication. It was through the intervention chiefly of R. Chrobak and his influence at Court and the persuasive personality and charm of von Rosthorn that the setting up of a special laboratory was made possible. Amongst the latest technical facilities first to be used in this laboratory was the Jung Tetrander microtome which enabled Schottlaender to cut and demonstrate sections of the whole uterus to the extent of 10 cm. and more, as well as of the placenta. These he took much pride in demonstrating. The longitudinal and transverse sections of the entire uterus were later to be reproduced in Schottlaender and Kermauner's book on carcinoma of the uterus.

Kermauner tells us that although Schottlaender's major scientific interest was rooted in gynecological and obstetric pathology, he was also interested in general pathology and its relation to clinical medicine and surgery: in the Abderhalden reaction, which he elaborated, and in general serology and endocrinology. According to Kermauner, he was a meticulously careful and thorough worker, absolutely reliable and "painfully" precise. Hesitant to commit himself to a



FIG. 1.

decision to which he could not bring positive support, he preferred to make no statement rather than venture a false diagnosis. However, when he did commit himself to a diagnosis, it withstood all criticism, subsequent clinical observation of the patient, proving him correct.

Schottlaender introduced routine systematic histologic examination of all excised tissues and organs including spontaneously discharged tissue particles. In an early publication it was my privilege to call attention to this routine and thorough laboratory examination, which I observed at first hand in this laboratory. Abraham Flexner was much impressed with the work he saw at this laboratory and apparently at the instigation of Schottlaender surprised me by requesting a reprint of my article shortly after his return to New York. Flexner had gone abroad to study medical schools and their curricula and organization. His report was the basis of reclassifying the medical schools of the U. S. A.

Schottlaender was most methodical in keeping protocol records of every bit of tissue submitted to his laboratory and the extirpated female genital organs were examined with the greatest scrutiny and completeness, many sections taken of the same specimen when necessary and no time or labor spared to establish a precise histopathological diagnosis.

It is of passing interest that Schottlaender valued these painstaking examinations so highly that he allocated his University salary to pay two technicians and from his private funds came the salary of an artist, H. Tegtneier, attached to his laboratory. The Professor was fortunately a man of means but this did not in the least divert his interest from the laboratory. On the contrary, I recall his habit of taking a very short time off for his midday meal consisting of a bread and butter sandwich and cup of tea and on many a day his work ended only when his charming wife called to remind him that his supper was cold and waiting for him. Schottlaender's devotion to his pupils knew no bounds. He gave up many hours, always cheerfully, to revising manuscripts of his pupils on problems proposed by him besides supervising and guiding the work itself.

On one occasion as the Professor was introducing me into the interpretation of the microscopic sections, each of us peering into the microscope, I suddenly became aware of someone's presence in the room. It was Frau Professor Schottlaender who came to call for her husband to take him to the opera for which they were already nearly an hour late. The Dolly sisters were to dance and the Frau Professor was fascinated by them. I felt like the culprit responsible for her disappointment. My teacher apologized and went to the opera, but I resolved not to be the cause of his discomfiture in the future if I could help it.

Schottlaender threw himself into his work and did not spare himself when engaged in teaching. He attracted a great many students from all over the globe whom he received as friends. It is no wonder that anyone coming under his influence and working in his laboratory inevitably imbibed the spirit of dedication to science.

Kermauer informs us that one of Schottlaender's main early interests was the study of the fate of the Graafian follicle which he elucidated with such clarity that it became common knowledge. Other interests in normal anatomy concerned

themselves with the observation of follicles containing multiple ova and multi-nuclear ova besides the determination of the duration of gestation as indicated by the histological findings and changes of the fetal blood. Among his important contributions is the demonstration, long before von Recklinghausen, of adenomatous elements in myomata. He was one of the first to demonstrate ovarian tuberculosis; he frequently referred in his discussions to adenomyoma, to changes of the lymphatics in dermoid cysts and reported his observations of uterine sarcoma. His clarification of erosion of the cervix was especially telling in the controversial discussion of this lesion. His thorough and critical review of Pfannenstiel's monograph on diseases of the ovaries brought to light many newer interpretations only realized years after its publication. Malformations occupied his attention, especially the relationship between the Wolffian duct and the uterus.

Schottlaender's most import work was concerned with uterine carcinoma published in collaboration with Kermauner in 1912. Of this work Kermauner says: "The indescribably painstaking gigantic work of making the histologic sections was all his own" (Schottlaender's). Later Schottlaender emphasized the early diagnosis of cancer and the changes of carcinoma during and after radium treatment. Schottlaender writes in the Preface to his book on Uterine Cancer that the idea of the book originated with Alfons Von Rosthorn who was to have written the anatomical and clinical parts while Schottlaender's job was to describe the histological findings. Death having robbed him of his original collaborator, Fr. Kermauner stepped into the breach and the book was dedicated to their Teacher and Chief. The work was actually begun at Grätz, was continued at Heidelberg and completed in Vienna December, 1911. The material included cases from the Clinics of these three cities from 1899 to 1910. The first reports on uterine cancer were made at the German Gynecological Congress in 1907 by von Rosthorn and Schottlaender, though the former had presented their findings the year before. The entire series upon which the book is based was 677 cases of uterine carcinoma. But only 135 cases are described besides five cases of vaginal cancer.

Schottlaender speaks of not lacking in assistance during the preparation of the book. But "whether they succeeded in utilizing outside help as well as their own to best advantage so that the book may prove useful and be alive will depend on the verdict of our colleagues." Schottlaender ends his Preface with these words: "Naturally, at the conclusion of our laborious task, our fondest hope is that it may bear fruit. *ut sint inter folia fructus!*"

The most important practical result of Schottlaender and Kermauner's work on Cancer of the Uterus was and still is the formulation of criteria of carcinoma of the uterus in its incipient stage while yet *in situ*. Based on the careful study of the abundant cancer material in his laboratory, Schottlaender and his associates and pupils were able to arrive at certain diagnostic conclusions which establish the presence of early carcinoma.

The question much discussed in the first decade of the present century concerned itself with the differentiation of metaplastic, non-malignant epithelial

changes from carcinomatous epithelium and from an atypical epithelium suspected of sooner or later developing into a full-fledged infiltrating carcinoma. To this differentiation between benign metaplastic epithelium and malignant epithelium, Schottlaender and his school devoted special attention.

The point of greatest value to the pathologist in the study of advanced growths is the contrast seen at the borderline of the cancerous invasion. For at the outskirts of the carcinoma may be seen the changes induced in otherwise normal epithelium by the invading cancer. The appearance of an incipient cancer according to Schottlaender is produced by the so-called storm troops or "shock troops" which attack the healthy tissue bordering upon it. The cancer at this point has the characteristics of the primary focus and here it may best be studied.

Schottlaender and his associates and pupils Schauenstein (8) and Pronai (9) were struck with the morphological changes seen at the visible borderline between carcinoma and apparently healthy areas of the vaginal portio and described these changes which they held to be characteristic of early cancer. If the cells showed marked aberrance or atypicalism in an area of epithelium, no matter how small, conforming in all respects to the criteria of cancer they regarded the particular focus as malignant. These criteria are briefly given as follows:—

1. Marked atypical epithelium arranged in many layers.
2. The individual cells differ from each other in respect to size, shape, arrangement and in regard to their chromatin content.
3. The absence of a membrana propria.
4. The presence of giant nuclei or of giant and multinucleated cells.
5. Atypical mitosis is common.

In view of the later development in cancer diagnosis as promulgated by Papanicalaou which focused on the female genital sphere, it is interesting to recall the present writer's conclusion in his first publication of 1910 (10), to wit: The important criteria in these early cases lie not so much in the relation of the cell nests to the stroma, the depth or extent of epithelial invasion, or evidences of surrounding inflammatory changes, as in the intrinsic morphology of the epithelial cells."

The incipient stage was conceived as a preclinical stage of cancer in situ not yet enough advanced to the point where it could be detected by inspection and palpation. At this stage only routine, systematic microscopical examination could reveal its presence. Somewhat later development and growth of this cancer focus could be diagnosed by the ordinary gynecological examination.

The histological diagnosis of cancer had been well established. But the approach to the problem of early diagnosis and criteria of judging cancer in its incipency was the unique contribution of Schottlaender and his followers.

I had the good fortune of being admitted to the laboratory of the II Universitat Frauenklinik as a voluntary assistant in early 1909. After an apprenticeship of six months, the Chief felt I had acquired sufficient knowledge of morphology to warrant my undertaking an "arbeit". When asked about a choice of work I decided upon study of the incipient stages of uterine carcinoma.

Schottlaender placed at my disposal three pathologic specimens which he thought were admirably suited for this purpose. The results of this work were reported in detail October 1910 (10). It was the first time this particular topic appeared in the American literature and in the English language.

The opening sentence of this paper is of interest in light of so much continuous discussion after a period of nearly a half century. It began thus, "The diagnosis of incipient carcinoma and the mode of its propagation are matters concerning which there is still a wide variance of opinion. The purpose of this paper is to offer a contribution to this subject as determined by the study of three cases."

Uterine cancer had already occupied considerable attention of gynecologists at the end of the last century.

An intensive study of uterine cancer had begun with G. Winter in 1891. It was followed by A. Gusserow also 1891 and W. D. Haggard, 1897, and Duhrssen in 1899. The first authentic book on cancer of the uterus in America appeared under the authorship of Thomas S. Cullen (11). Cullen's book preceded Schottlaender's and Kermauner's book by twelve years. It is remarkable that Cullen, a foremost gynecologic surgeon made it his special task to collate the pathological material of the Johns Hopkins Gynecological Department headed by Howard A. Kelly whom he succeeded. Cullen observed histological changes at the periphery of cervical carcinoma which were in some but not all respects similar to those described by Schottlaender and his pupils from 1907 to 1910. In 1921, Cullen (12) reported an early squamous cell carcinoma of the cervix in which he showed microphotographs similar in all respects to those published by the writer in 1910 and by Schottlaender and Kermauner in 1912. Of this case Cullen says, "the second scraping yielded a most beautiful example of early proliferation of the epithelium associated with the development of a squamous cell carcinoma. In fact, it is the earliest case of squamous cell carcinoma of the cervix that I have ever seen." On opening the uterus, Cullen found "a submucous fibromyoma 1.5 cm. long. Near the internal os was a small papillary growth 9 millimeters long, 3 millimeters broad, all that remains of the small carcinoma that started near the internal os."

Cullen's observations in 1921 corroborated those of Schottlaender and they were still further confirmed by the later reports of Te Linde and others. But the most far-reaching support for the histologic criteria of early carcinoma was given by Papanicalaou and Traut in 1941 (13). These authors in their studies of exfoliated epithelium contained in the vaginal smear, found "abnormal cells whose most characteristic feature is the atypical form and structure of their nuclei. These often are very large, far surpassing normal size. The chromatin frequently shows a characteristic distribution in the form of conspicuous granules and of one or more small nucleoli. It is not unusual to find cells with more than one nucleus. This is probably the result of abnormal fragmentation or amitotic division. The cytoplasm also shows abnormal changes. It is often dense and hyperchromatic particularly in the cells of the basal type. Such cells may appear singly or in compact dark staining clusters. Their form and size vary greatly." "A commonly found, very characteristic cell type is an extremely elongated one resembling a smooth muscle fiber."

The cells described by Papanicolaou and Traut were all depicted in Schottlaender and Kermauner's book in 1912. The conclusions reached independently by such expert observers as Papanicolaou and Traut could not but lend significant support to the claims of the older authors for the characteristics of neoplastic epithelium.

These histological characteristics of cancer are now almost universally recognized. Schottlaender made his early observations with a monocular microscope. In 1909 he bought one of the first two microscopes with Leitz apochromatic lenses made by Schütz A. G. Cassel, Germany. The second microscope he ordered for me and it is still in daily use today. One can only wonder how much more could have been discovered if the *electron microscope*, *automatic scanning microscope* and the *interference microscope of Baker* or the *contrast phase microscope* of today were available a half century ago.

Schottlaender's second chief contribution was on malignant metastases of genital cancer spreading to other viscera; and vice versa, metastases from primary cancer of other organs and secondarily involving the female genitals. This chapter was published in the supplement to Von Nothnagel's Special Pathology and Therapy. In this publication Schottlaender surveyed the entire literature with critical appraisal. Of the latter work Kermauner writes: "It is an enduring monument to Schottlaender, which has seldom been equalled serving as a model to succeeding generations."

In connection with Schottlaender's and Kermauner's book on Uterine Cancer, my good friend and fellow student of Schottlaender, Josef Novak, recalls R. Paltauf's comment: "This work of Schottlaender and Kermauner is the tombstone of the pathology of uterine carcinoma. There is nothing left for others." These predictions were realized many years after Schottlaender's death. It is still true that very little has been added in the past forty years to the histopathology described in Schottlaender and Kermauner's monumental volume on uterine cancer. If advances in cytochemical investigation can be recorded it may be that Schottlaender's work has stimulated much of this progress. But if it has remained so long unappreciated, Schottlaender's contribution is another example of the many that can be cited in this connection which lay unrecognized and dormant for decades until some force brought it to life again.

Kermauner concludes his necrology with the statement that Schottlaender was a man of extraordinary refinement and sensitivity, tactful, genial and amiable, who withdrew from the daily strife of living but never fled from any challenge, which he faced energetically. According to his close collaborator, "Schottlaender was shy and did not make lasting friends readily but once the ice was broken his friendship endured all storms. He was true as gold, a man who never forgot friends of his youth."

In the many necrologies published, there was the same refrain about his character. In Halban's language, "everyone who had the occasion to come in contact with him had the feeling that he was dealing with an exceptionally fine human being who worked for the sake of the work itself without thought of honor, position, or ultimate gain; moreover, that his scientific work was devoid of unselfish motives and of an enduring quality."

The Biographic Lexicon of famous physicians published in 1933 of the previous 50 years, edited by I. Fischer, Band II, Berlin (Urban and Schwarzenberg) expressed the same high estimate of Schottlaender, the man and scientist.

E. Wertheim regarded Schottlaender's death as a heavy loss to gynecology and referred to him as a recognized authority. Robert Meyer quoted by Wertheim said of Schottlaender's work on cancer of the uterus that "such thorough and careful treatment of the subject had not been equalled with regard to uterine cancer nor for that matter concerning any other tumor. Schottlaender was a brilliant example of how one can derive from specialized concentration on a single lesion new and fruitful viewpoints of importance for the whole profession of medicine."

E. Wertheim expressed sincere satisfaction that Schottlaender remained in the Klinik after von Rosthorn's untimely death in 1909. Wertheim was not aware of Schottlaender's quandary which he confided to me at the time of the death of his beloved chief von Rosthorn. When Wertheim succeeded the latter, Schottlaender was not sure whether the new chief would retain him. I knew Wertheim in 1909 and met him again in 1914. His high appreciation of Schottlaender's worth, as revealed in his necrology of 1917, was a pleasant surprise to me. Though Wertheim was a "natural born" surgeon, he was essentially a scientist also and "he now was able to have the collaboration of a scientific worker of the first order in Schottlaender" whom he invited in the most generous terms to continue as head of the famous laboratory. Wertheim, be it said to his credit, acknowledged that "from the beginning of his assuming the leadership of the position vacated by von Rosthorn with whom Schottlaender enjoyed the most friendly relations and cooperation, he felt it as his obligation toward Schottlaender to do everything in his power to maintain the same personal relationship with this outstanding person."

It is thus evident that Schottlaender's misgivings as to Wertheim's attitude and intentions toward him were actually unfounded. Wertheim concludes his estimate of Schottlaender by saying that "his influence on the II University Frauenklinik will always remain exemplary and we will always accord von Rosthorn great credit for succeeding in attracting this great force (Schottlaender) to the II Frauenklinik."

A. Martin regretted not being able to accommodate Schottlaender in his private clinic for lack of space and urged him to go to Heidelberg to join von Rosthorn. The latter never lost an opportunity to thank Martin for this *gift*. Martin considered Schottlaender to have a solid preparation for academic work and looked forward to "seeing this man realize the highest expectations of a scientist and teacher."

Three months after I began studying with Professor Schottlaender, I felt I was not making enough progress to warrant continuing the course in gynecologic and obstetric pathology and decided to turn my attention to clinical and anatomical work. It was no easy step to take but I decided to tell the professor of my decision. After thanking him for all the trouble he took in trying to educate me in microscopic pathology and explaining my position I was about to take

leave when he placed both hands on my shoulders and said: "Herr Rubin, I have been at this work thirty years. Is it fair for you to expect to learn in three months what I have acquired in thirty years? Stay on and let's try it some more." I did and can never stop being grateful for that unforgettable gesture of kindness and lesson in humility.

This incident does more than indicate the generous attitude of a teacher to a pupil. It marks the date of his first interest in gynecological pathology which makes him probably the first pioneer in this field. When finally I said good-bye at the end of a year, I stammered my gratitude and he sent me off with these words: "Schaffen Sie nur wissenschaftlich" Just carry on your scientific work!

Four years later, February 1914, I called upon Professor Schottlaender and asked him for permission to work in his laboratory for another year. Upon his inquiry about my interests at the time, I said I would like to study the histology of the corpus luteum during the different phases of the menstrual cycle. Another objective was to do some experimental animal work and research in the hope of arriving at a non-operative method of diagnosing with the aid of the x-rays and a contrast medium injected into the uterus, the presence of sub-mucous fibroids. This variety of fibromyoma had been found to be refractory to x-ray treatment of fibroids—a method of treatment much in vogue at that time, following A. Schoenberg's results with x-rays which showed that the submucous tumor was unaffected by the irradiation treatment. Many gynecologists had stopped doing hysterectomy for a while in favor of x-ray therapy. If the uterus contained a submucous myoma and its presence could be demonstrated, time could be saved by doing a hysterectomy at once.

As to my first purpose, Professor Schottlaender told me I needn't bother about the corpus luteum study because R. Meyer and Carl Ruge had settled that question. He showed me the issue of the *Zbl. f. Gynak* 1913, 73, 966-970 in which these investigators published the results of their studies, and established as it seemed then for all time the cyclical changes in the corpus luteum corresponding to parallel changes in the endometrium. R. Schroeder working simultaneously with this problem came to the same conclusions which he published in the *Monatsch. f. Geb. u. Gyn.* Bd 38, Heft 1.

As to the second purpose of my stay in Vienna, Schottlaender approved of the idea and placed the facilities of his laboratory at my disposal. In the course of three months the preliminary work was accomplished and published out of his laboratory in the *Zentralblatt f. Gynecology*, May 2 xxxviii, No. 18. Joseph Novak translated my paper into German. It formed the basis for further studies of tubal patency and non-patency (hysterosalpingography).

As a side-light of the teacher's interest in a pupil for further study and instruction, I may be pardoned for relating a minor incident which took place at this visit in 1914. Professor Schottlaender placed a half dozen slides in succession under the microscope and asked me for the diagnosis. Fortunately I was able to identify the lesions. Among them was a small chorion-epithelioma of the uterus, an adrenal rest in the mesosalpinx and "adenomyometritis" as it was then called. This test of my progress pleased him and he said it was not necessary



FIG. 2.

for me to spend a whole year in Vienna, that I could do the work in New York. Thanks to Doctor Eli Moschowitz I was able to continue at the laboratory of Beth Israel Hospital my histologic studies which had begun there in 1910.

Schottlaender occupied a beautiful blue house in the Hohe Warte in the outskirts of Vienna. It was unostentatious outside as were the interior decorations. He had a spacious garden adjoining the magnificent estate of Baron de Rothschild. It afforded the quiet and charm the professor needed in the hours he could spend away from his laboratory.

I cherish the memories of the most pleasant hours spent in the Schottlaender home, the warm hospitality of the Professor and his wife and the companionship of his two sons who were but a few years younger than myself. What has become of them I do not know. I last heard from Frau Schottlaender in 1937. She was living in Reval, Esthonia, and kindly sent me the photograph of her husband shown here (Fig. 2). The photograph was made when the Professor was about 40 years old. He was 49 when I worked in his laboratory. At that age he seemed

to be much more mature. He was an admirable speaker and I was charmed to listen to his discourses at the meetings of the Physician's Society, understanding after a long while not only every word but every sentence! Under his stimulus I had learned medical German by translating Bumm's obstetrics from cover to cover so that after a year I became quite conversant with the German language though in my case it had an obstetrical flavor immediately recognized by anyone who listened to me. Professor Schottlaender never gesticulated during his discussions before the Medical Society or during his lectures to students, speaking in a calm voice without referring to manuscript or notes. His knowledge of the subject under discussion was illuminating at all times and his colleagues listened attentively when he spoke. He never sought by gesture or emphasis to impress the facts which always formed the basis of his statements. He was truly exemplary as Wertheim characterized him. In the opinion of his famous contemporaries, Schottlaender was unique in his time or perhaps any other time.

Now after the passage of forty years, their estimate and predictions of the enduring quality of his scientific contributions appear to be fully realized.

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IDIOPATHIC NON-SPECIFIC FIBROSING RETROPERITONITIS CAUSING BILATERAL URETERAL COMPRESSION

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During the past nine years, approximately fourteen cases of bilateral extrinsic ureteral compression due to a non specific retroperitoneal inflammatory process have been reported. Similar unpublished cases have undoubtedly been observed. It is imperative for clinical recognition and effective treatment that this condition be fully accepted as a disease-entity, although its pathogenesis and etiology have not yet been determined. The basic therapy in previously reported cases has varied, as have the results.

We wish to present a fifteenth case of bilateral ureteral compression due to non-specific idiopathic fibrosing retroperitonitis successfully treated by bilateral ureterolysis and with antibiotic and radiotherapy. The trials and tribulations encountered in the management of this case make it unusually interesting and instructive.

CASE HISTORY

(#44374) A 44 year old male of Italian descent was first admitted to The Mount Sinai Hospital on April 4, 1955 with a chief complaint of low back and bilateral loin pain of one and a half years' duration. There was no previous history of urinary tract infection, dysuria, pyuria, chills or fever and there was no history of hypertension, edema or ascites. In January 1955, the patient was hospitalized elsewhere for orthopedic care. In view of the meager orthopedic findings, a therapeutic test of bed rest and traction was applied, unsuccessfully. In the next three months the patient had agonizing bilateral costovertebral non-colicky pain with nausea and faintness. Except for scrotal enlargement attributed to a hydrocele, a review of other systems and the past history were non-contributory. Negative urine examination and a normal blood urea nitrogen were obtained three days before his entry to The Mount Sinai Hospital. At that time intravenous and retrograde pyelograms performed to rule out a tumor of the right kidney with involvement of the inferior vena cava, showed dilatation of both upper urinary tracts. The lower ureters were not seen. Cystoscopy revealed a normal urinary bladder and catheters were passed with ease to both renal pelves and yielded a bilateral hydronephrotic flow.

Physical Examination: The patient did not appear to be in acute distress although he looked chronically ill. The temperature was 98.6° F.; respirations, 20 per minute; pulse, 72 per minute; blood pressure, 180/110 mm. Hg. The head, eyes, ears, nose and throat were negative except for slight exophthalmos. The heart and lungs were normal. On abdominal palpation, the liver was felt two finger breadths below the costal margin, and the spleen one finger breadth below the costal margin. The rectal examination disclosed a two times enlarged nodular benign prostate. There was moderate left ankle edema and the genitalia showed bilateral scrotal edema and hydrocele, the right being larger than the left with some pain and tenderness.

Laboratory: Hemoglobin, 8 grams per cent; white blood cell count, 8,850 per cu. mm. with a normal differential count. There was anisocytosis, poikilocytosis and hypochromia of the

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FIG. 1. Intravenous pyelogram before admission showing non-visualization of left kidney and dilatation of right upper urinary tract.

red blood cells. Blood urea nitrogen, 55 mg.%; fasting blood sugar, 71 mg %; total protein, 6.8 grams %; albumin, 2.9 grams %; globulin, 3.9 grams % with elevated alpha I globulin; calcium, 9.2 mg %; phosphorus, 7.7 mg. %; total cholesterol, 175 mg. %; alkaline phosphatase, 7.8 King Armstrong Units; acid phosphatase, 3.2 King Armstrong Units; sedimentation rate, 128 mm/hr; blood Wasserman, negative. Urine showed a specific gravity of 1.016 and was alkaline with a faint trace of albumin and no sugar. Many red blood cells, 15-20 white blood cells and 1-2 white blood cell clumps per high power field were seen. Patient's blood type was O rh positive. A complete hematologic work-up was performed. The findings of the peripheral blood were consistent with his anemia. The sternal marrow smear was reported as being negative but compatible with a lymphomatous disease. Chest x-ray revealed several fine Fleischner lines in the basal portion of the right lung with partial obliteration of the right costophrenic sinus. The lung fields were otherwise normal. Heart and mediastinum were also normal; there was no hilar lymph node enlargement. Cystogram of the bladder was normal in size and contour. There was no evidence of intrinsic or extrinsic organic lesions. A skull and long bone x-ray survey were essentially negative, and showed no evidence of multiple myeloma or metastatic disease.

Course: The patient was practically anuric on the first day of admission. On April 6, 1955 he was recystoscoped and very little urine was obtained from the bladder, which was negative. Catheters were passed easily for the full distance to both renal pelvis and hydro-nephrotic flow of clear urine was obtained bilaterally. The ureteral catheters were left



FIG. 2. Left retrograde pyelogram before admission showing dilatation with abrupt non-visualization of ureter.

indwelling and the patient diuresed about 4000 c.cs. of essentially clear urine for the next ten days, after which his urinary output declined to between 1300 to 2400 c.c. per day. His blood urea nitrogen fluctuated from between 83 to 19 mg.% following this manipulation. Since admission, the blood urea nitrogen had never been consistently within normal limits to warrant performance of an excretory urogram.

On April 13, 1955 the patient spiked a temperature of 105. Blood culture grew *B. Aerogenes*. A right nephrostomy was done two days later in order to obtain better drainage, the working preoperative diagnosis being retroperitoneal lymphosarcoma. During this procedure, it was observed that Gerota's fascia was thickened. The fat appeared to be indurated and edematous. The induration increased as the dissection was directed towards the ureter. The periureteral tissue was represented by a mass of woody induration with dense longitudinal bands of fibrous tissue. There were enlarged periureteral lymph nodes incorporated in the inflammatory tissue. The upper and middle third of the ureter was then mobilized. There was difficulty in initiating this mobilization of the kidney. A ureterotomy was performed in order to bring a nephrostomy tube into the pelvis with the use of a Kimball hook. A lymph node near the medial border of the psoas muscle about two inches below the ureteropelvic junction was excised for biopsy. During this last mentioned maneuver bleeding from branches of the inferior vena cava could not be controlled with the usual methods. Two large clamps controlled the hemorrhage and were left in situ. The wound was closed



FIG. 3. Intravenous pyelogram following bilateral nephrostomy showing dye in bladder.

about the clamps, which were removed after seven days. The pathological reports of the biopsied tissue and lymph node stated "fat tissue with lymph node showing acute and chronic lymphadenitis". On April 22, 1955 because of a rising blood urea nitrogen in spite of nephrostomy, two number five French ureteral catheters were passed into the left kidney and made indwelling. During the next few days the patient's urinary output measured approximately 200-300 c.c. of urine daily via the left ureteral catheters. The right nephrostomy tube continued to put out a good quantity of urine daily. His temperature remained within normal limits. Antibiotics administered during these periods consisted of terramycin, combiotic and Gantrisin[®]. On April 17, 1955, after consultation with the Radiotherapy Department, it was decided to give this patient two separate courses of radiotherapy of approximately 600 r in air with 200 KV radiation to each flank with anterior portals of 20 cm. x 10 cm. to the right side and 20 cm. x 15 cm. to the left side. These factors yield a depth dose in the region of the ureters of approximately 300r. However, despite the relief of the mechanical obstructive uropathy, and the return to normal of his blood urea nitrogen, the patient appeared chronically ill. He was therefore given an extensive work up including a GI series and barium enema to rule out an unsuspected primary source for retroperitoneal inflammation or neoplasm. A gingival biopsy was done to rule out amyloidosis. These examinations were all negative. There was now a strong suspicion that we were dealing with that disease-entity best described as "*idiopathic non-specific fibrosing retroperitonitis*".



FIG. 4. Left gravity pyelogram showing dye entering bladder.

On May 5th, 1955 a left nephrostomy was performed. The posterior surface of the kidney was approached first. There appeared to be a pseudomembranous layer of organizing scar tissue, which was dissected away and the ureteropelvic junction was exposed inferiorly. The ureter showed compression and was encased in a dense fibrous sheath. This sheath was split along the lateral surface of the ureter over a grooved director and was mobilized freely as far as the pelvic brim where it gradually assumed a more normal appearance. A portion of the fibrous tissue surrounding the upper third of the ureter was removed for biopsy together with an adjacent lymph node. The pathologic diagnosis was "lymph node showing chronic inflammation; surrounding tissue showing fibrosis and non-specific acute and sub-acute inflammation". A segment of the 12th rib taken to exclude multiple myeloma showed "no unusual features".

The postoperative course following this left nephrostomy and ureterolysis was smooth and uneventful. Frei test for lymphogranuloma venerum was negative. An intravenous pyelogram performed one week after operation showed prompt excretion bilaterally. A small amount of dye was seen throughout the right ureter and entering the bladder. The left ureter was not visualized.

On May 31, 1955, the right nephrostomy tube was clamped. On June 7, 1955, the second course of radiotherapy was started on the left side. Because of poor visualization of the left ureter, a ureteral catheter was passed. It went up easily to the left pelvis and was made indwelling for four days. On June 18, 1955, the patient developed a left epididymitis which



FIG. 5. Split film of first follow-up intravenous pyelogram in August 1955.

was treated successfully with penicillin. At about this time, the left ureter was determined to be patent by a gravity antegrade pyelogram. The left nephrostomy tube was clamped off on June 24, 1955. Patient voided well with a daily urinary output of over 1500 c.c. The left nephrostomy tube was removed on June 28, 1955 and the wound remained dry after two days and healed well. An intravenous pyelogram on July 1, 1955, showed prompt appearance of dye in both upper urinary tracts with good concentration. The upper portion of the collecting systems of the right kidney was somewhat dilated. The right ureter was not seen. There was no dilatation of the collecting system of the left kidney and only the uppermost portion of the left ureter was visualized. On July 2, 1955 the patient was discharged from the Mount Sinai Hospital with a clamped off right nephrostomy tube in situ and his general condition greatly improved.

On July 27, 1955, the patient was readmitted to The Mount Sinai Hospital because of right flank pain, chills and fever of four days' duration. During this interval of twenty-five days between discharge and readmission, the patient noted that his urine had been intermittently cloudy but he remained asymptomatic until the onset of these symptoms. He had been treated at home with penicillin and terramycin; after which his fever subsided but right flank pain persisted.

The temperature was 102.2°F; the pulse was 96 per minute; his respirations were 20 per minute and his blood pressure was 110/70 mm. Hg. Physical examination was essentially

negative except for the genitalia which showed the left testis and epididymis to be still very much indurated and non tender, but the previously noted scrotal edema, and ankle edema were gone. There was a well healed left CVA scar and the right nephrostomy tube was still clamped. His hemoglobin was 10.4 grams per cent. His white blood count was 9700 per cu. mm. Differential was normal. Blood urea nitrogen was 32 mg.%, carbon dioxide combining power was 24 mEq/liter, chloride was 103 mEq/liter, sodium 142 mEq/liter, potassium 4.7 mEq/liter. Bladder urine showed a specific gravity of 1.020, acid reaction, albumin and sugar were negative. Many white blood cells per high power field and occasional white blood cell clumps were seen. The urine culture grew *B. Coli* and *B. Proteus* both resistant to achromycin and streptomycin but relatively sensitive to Furadantin[®].

On the day of admission, the nephrostomy tube was opened and 75 c.c. of grossly purulent urine was drained. The nephrostomy tube was left open and drained into a bedside bottle. After two days of Furadantin therapy, and nephrostomy drainage, the patient's temperature returned to normal and his urine became fairly clear. An intravenous pyelogram showed a radio-opaque stone in the right renal pelvis in the region of the nephrostomy tube. There was bilateral function with delay of visualization of the right side. The patient was placed on a through and through continuous irrigation with Suby G. solution. In an attempt to dissolve the stone this solution was run in through a cystoscopically introduced ureteral catheter and drained out through the nephrostomy tube at a rate of approximately 30 to 40 drops per minute. The patient tolerated this irrigation very well without any untoward reaction. Several days after the irrigation, x-rays showed the stone reduced approximately to one-third its original size. However, the irrigation was kept on for a total of sixteen days. An x-ray then showed that the stone had disappeared and the ureteral catheter was removed. The nephrostomy tube was removed two days later and the wound healed promptly. The patient remained asymptomatic although four days after removal of the nephrostomy tube, an intravenous pyelogram showed definite dilatation of the upper urinary tract. The ureter was not outlined. In view of the increased dilatation of the upper urinary tract, two number five ureteral catheters were again passed into the right renal pelvis. There was approximately 15 c.c. of purulent urinary retention which grew out *B. Coli* and *B. Proteus* on culture. The catheters were left indwelling for approximately four days and a few days after removal an intravenous pyelogram disclosed prompt function bilaterally with no improvement of the dilatation of the right upper urinary tract.

Since June 21, 1955 the patient had been placed on meticorten 10 mgs. three times a day in order to help reduce any further inflammatory scarring type of process. The drug was discontinued on August 25, 1955. At this time a repeat examination of the serum globulin pattern showed all components increased especially the alpha globulin but the latter was slightly reduced over the initial findings. Patient was given an acid-ash diet and furadantin to which his infection was most sensitive. His general condition was much improved and he was relatively asymptomatic. He was discharged from the hospital on August 13, 1955.

When seen in February 1956, the patient was well and had returned to his usual occupation. Blood chemistries revealed a blood urea nitrogen of 15 mg.%; carbon dioxide, 59 vol.%; chloride, 106 mEq/liter; sodium, 141 mEq/liter; potassium, 4.7 mEq/liter; sedimentation rate, 18 mm. 1 hr; total protein, 8.0 grams %; albumin, 4.3 grams %; globulin, 3.7 grams %.

Excretory urograms performed in February 1956, and January 1957 showed prompt bilateral visualization. The left upper tract was normal. The right kidney showed moderate pyelectasia.

On January 26, 1957 physical examination was negative except for the right hydrocele. There were no urological symptoms no backache, no abdominal pains. A moderate number of white blood cells were present in the urine. The patient looked robustly healthy and was working fully in his occupation as a furrier. It is now two years postoperative.

Pathology. "Histologically, broad areas in this retroperitoneal tissue are composed of dense bundles of collagenous fibrous tissue which are almost keloidlike and are poorly nucleated. The nuclei are small and of the usual fibrous connective tissue type. In other

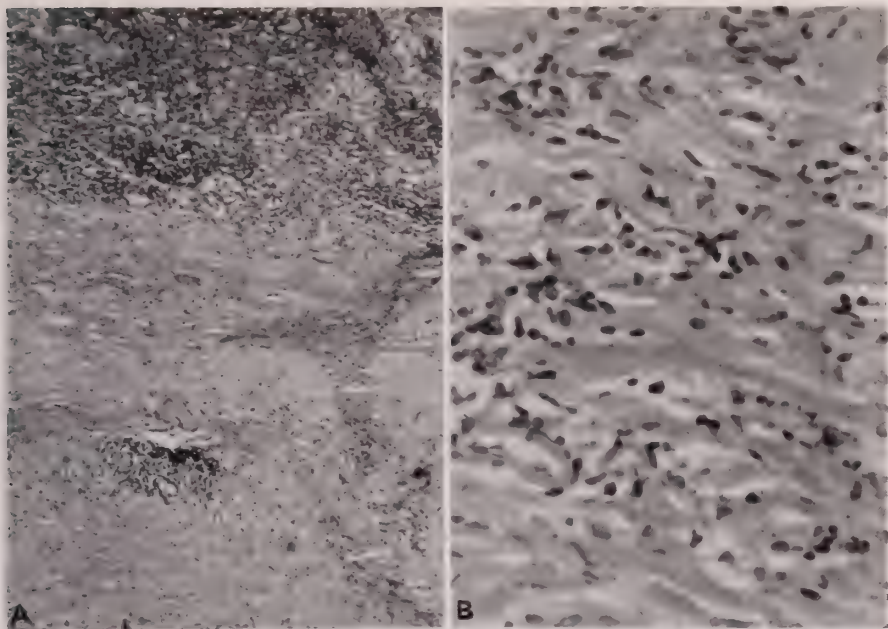


FIG. A. Retroperitoneal tissue; low power; showing edge of lymph node, poorly cellular keloid like fibrotic areas and foci of non-specific cellular inflammation.

FIG. B. Retroperitoneal tissue; high power; showing dense collagenous tissue with small darkly nucleated fibrous cells, fibroblasts with large vesicular nuclei, lymphocytes, wandering cells and occasional eosinophiles and occasional polynuclear leucocytes.

areas, or in foci within the denser areas, there are zones of varying size which are more prominently cellular. These show the presence of fibroblasts with regular nuclei, small dark round cells, wandering cells and occasional eosinophiles and occasional polymorphonuclear leucocytes. The latter show no microabscess aggregations, though the round cells may be grouped into small follicles. The lymph nodes show hyperplasia with prominent follicles. There are no stigmata of specific inflammations such as are seen in lues, tuberculosis or Hodgkin's disease. No nuclear inclusions or parasites are found. There are no evidences of neoplasia such as is seen in the lymphomas, lymphosarcoma, reticulum cell sarcoma or metastatic carcinoma or fibrosarcoma.

Diagnosis: Non-specific chronic fibrosing retroperitonitis containing:

1. Foci of subacute and acute inflammation
2. Non-specific lymphadenitis."

REVIEW OF LITERATURE

Ormond (1) should be credited for his initial observations of the condition under discussion, first published in 1948. Since then about 14 cases have been reported of a clinical-pathological entity which recognized: (a) the extrinsic nature of the ureteral compressions, (b) the absence of any primary intrinsic ureteral stricturing disease, and most important, (c) the presence of a non-specific inflammatory process in the retroperitoneal tissue which begins not in the immediate periureteral connective tissue but is more diffuse and by extension reaches to and envelopes the ureter or ureters secondarily.

Ormond's (1948) first case showed on postmortem a diffuse retroperitoneal

mass extending from the sacral promontory to both kidneys and ensheathing both ureters, the aorta, the vena cava, lymph nodes and nerves (1).

His second case, at operation, disclosed a retroperitoneal, flat mass with indistinct lateral margins covering the promontory of the sacrum and enveloping both ureters.

In the Ewell and Bruskewitz (2, 3) case there was a thickening of Gerota's fascia and marked fibrosis of the perinephric fat on the left side and subsequent periureteral compression on the right. In Amselem's case (4) there were retroperitoneal bilateral ureteral compressions and fibrous adhesions. In 1952, Miller, Lipin, Meisel and Long (5) reported a case in which laparotomy showed a retroperitoneal, firm, slightly hemorrhagic mass extending from the kidneys down over the sacrum and imbedding both ureters. This mass was palpable abdominally as long as three years after operation which consisted only of biopsy without freeing of the ureters. The case of Oppenheimer, Narins and Simon (6) of periureteritis cured by radiotherapy is important therapeutically but is obviously not of this group.

In 1953 Bradfield (7) recorded a case in which abdominal exploration revealed a smooth firm rubbery mass, situated chiefly over the fifth lumbar vertebral body, obscuring the bifurcation of the aorta with extensions embedding the right ureter.

In 1954, Chisholm, Hutch and Bolomey (8) reported a case in which they demonstrated a thick sheath of coarse fibrous tissue originating from the psoas muscles bilaterally, extending across the vertebral column and ureters and up to the renal pelvis. In 1955, Raper (9) described three cases of oliguria and uremia due to obstruction of the ureters by an invasive type of fibrosis which seemed to originate around the main vessels on the post abdominal wall; one case involved tissues in front of the vertebral bodies and the mesentery of the jejunum. In 1955, Otani, Ginsburg and Averbuck (10) had an unreported case without compressive involvement of the ureters which showed "retroperitoneal inflammatory tumors". In 1955, Mirabile and Spillane (11) reported a patient with both ureters compressed by a broad band of inflammatory tissue. In 1956, Nannestad's case (12) showed diffuse retroperitoneal chronic inflammation with bilateral ureteral involvement.

In 1953, Vest and Barelare (13) reported on "Periureteritis Plastica" and demonstrated the dissimilarity between the entity they encountered in their four cases of unilateral compression of the ureter, and the Ormond type of cases of diffuse granulomatous retroperitoneal involvement. In their cases the periureteral inflammatory process involved only the immediate periureteral area, suggesting periureteral lymphangitis as the etiology. In 1956 Hejtmancik and Magid (14) reported a case of "Bilateral Periureteritis Plastica" in which each ureter entered an area of flat indurated plastic tissue which tho localized to the immediate periureteral area, also involved the parietal peritoneum. They pointed out that tho the entity of periureteritis plastica may be of a different etiology and pathogenesis than the entity of diffuse chronic fibrosing retroperitonitis, the clinical syndromes that these entities engender may be very similar. In our view

the important and *common* feature of the surgical pathological anatomy present in both of these entities is the extrinsic compression of the otherwise patent ureteral lumen. This compressive lesion lends itself to therapeutic "shelling out" of the ureter i.e. surgical ureterolysis resulting in the resumption of effective ureteral peristalsis and function.

PATHOGENETIC TERMINOLOGY

We have chosen to use the term *idiopathic non specific, fibrosing retroperitonitis*. The term *idiopathic* will emphasize the lack of a known primary focus of origin for the inflammatory involvement of that potential retroperitoneal space envisaged by Daseler and Anson (15) and Congdon and Edson (16) who demonstrated a renal fascia which encloses the kidneys, the abdominal aorta and vena cava along with both ureters.*

Our patient had been in robust health and neither the preoperative history, nor the subsequent course of now two years duration, nor the numerous gastrointestinal and radiological investigations have disclosed any primary disease focus. Chisholm (8) mentions such reported possibilities as regional ileitis, appendicitis, diverticulitis and ulcerative colitis. Like ours, almost all the reported cases are devoid of a primary focus. We have chosen the term *retroperitonitis* to emphasize the existence of more diffuse inflammatory involvement of the *retroperitoneal* tissue than that in the immediate periureteral area. This would bring it into better relationship with the so called pseudoneoplastic, "retroperitoneal inflammatory tumors" of Otani; and alert us to the necessity of *biopsied* evidence for the definitive differential diagnosis from any of the retroperitoneal tumors or neoplasms, i.e. Hodgkins disease, lymphosarcoma, reticulum cell sarcoma, fibrosarcoma and metastatic carcinoma and even tuberculosis.

The cases of urological complications, even uremia, are wonderfully salvageable if the *idiopathic* and therapeutically approachable inflammatory nature of this diffuse *fibrosing retroperitoneal disease* is more widely known and sought for and appropriately treated.

CLINICAL PICTURE

In regard to the clinical features of this disease: some have had the onset marked by prominent back symptoms treated orthopedically, even to the use of major immobilization procedures and herniated disc operation. Others have had the onset treated surgically for vague abdominal symptoms with palpable abdominal masses which were then found to be retroperitoneal and not intraperitoneal. Others have been initially treated by internists for vague nephritic symptoms with loin pains, poor health, anemia, edema, hyperglobulinemia and

* "At the lateral border of the right kidney, the anterior and posterior lamina of the (right) renal fascia fused to form a single subperitoneal connective tissue layer; at the mesial border the anterior lamina passed in front of the renal vessels, the inferior vena cava and abdominal aorta to become continuous with the corresponding fascial layer of the left kidney (16). The posterior lamina of the renal fascia passed behind the kidney and renal vessels to fuse with the fascial layers underlying the aorta and inferior vena cava and covering the psoas major and lumbar vertebral bodies."

urinary findings suggestive of the nephrotic stage of glomerulonephritis, multiple myeloma or the vena cava syndromes. Others have been suspected of having inoperable abdominal or retroperitoneal neoplasms and have been treated by radiotherapists without diagnostic histological proof. The more easily elucidated clinical symptoms have occurred in those first treated by urologists for symptoms of recurrent pyuria and obstructive pyelonephritis, or for oliguria and gradual or sudden onset of anuria or uremia. All the published cases have been correctly diagnosed however initially or finally by urologists with their appropriate investigations and procedures. Cystoscopy and ureteral catheterization with the easy passage of the catheters to the pelvis disclose a paradox: namely, a significant degree of ureterohydronephrosis without intrinsic obstructions, and proves the true compressive nature of the *idiopathic* and diffuse fibrosing inflammatory retroperitoneal process.

In our case, the clinical course was initially vague and not revealing. A robust, never sick, man began to have pain in his lower back which persisted for one year and during the next six months became so agonizing that he received orthopedic care at another hospital. There he showed positive, slight, bilateral leg raising tests and slight lumbosacral tenderness—but no costovertebral tenderness. There were no formed elements in the urine, which showed only a faint trace of albumen. After bed rest and orthopedic measures he was not improved. However the presence of slight pretibial edema and prominent scrotal edema with newly developed hydrocele, rapid blood sedimentation rate and hyperglobulinemia indicated that other than orthopedic factors were involved. Multiple myeloma was easily excluded by negative Bence Jones protein tests, by negative bone marrow tests and absence of bone x-ray findings. The suspicion of inferior vena cava syndrome, aroused by the non cardiac edema of the legs and scrotum, showed the indication for intravenous pyelogram to exclude right hypernephroma with renal vein and vena caval involvement. The urinary findings and blood urea were normal. Intravenous and retrograde pyelograms showed bilateral upper ureterohydronephrosis without visualization of either lower ureters. Retrograde ureteral catheterizations showed the first obvious important paradox—very easy passage of the ureter by the catheter yet rapid flow of clear (retention type) urine from the pelvis i.e. ureter patency yet hydronephrosis.

The suspicion of a retroperitoneal neoplasm—probably lymphosarcoma broad enough to involve both ureters—was engendered. The patient was then transferred to The Mount Sinai Hospital for further procedures. Radiotherapy and the possibility of a guarded, pessimistic prognosis were discussed. Between the time of the cystoscopy and the hospital admission he had developed severe oliguria—almost anuria. The blood urea had risen from 17 to 55 mg. %. Indwelling right ureteral catheter drainage was done and was effective. But the occurrence of chills with fever up to 105 degrees (enough to give the patient a positive blood culture of *B. aerogenes*) hurried the necessity for exploration. At right extra-peritoneal exploration, no obvious neoplastic or lymphosarcomatous mass was encountered. Thickening of Gerota's fascia and induration of the perirenal fat were noted. Broad retroperitoneal woody induration extending to the vena

cava were palpated. Mobilization of the kidney and freeing of the imbedded upper 2_3 of the ureter was done and ureteral catheter drainage and right nephrostomy were accomplished. Biopsy of the woody tissue and one of the lymph nodes revealed the non-specific, chronic fibrosing retroperitonitic nature of the ureter-ensheathing tissue. The possibility of this being a case similar to that described by Ormond (1) now became a reality and working hypothesis.

Radiotherapy was instituted because of the possibility that neoplasia (i.e. lymphomatous) was not altogether excluded and because of previous experience with a cured case of ureteral stricture with periureteritis (16). But a positive approach which would include bilateral ureterolysis was now visualized.

Happily, the same inflammatory process was proven histologically on the opposite side and bilateral ureterolysis has been effective albeit with dire calculus and other urological problems encountered and solved during the road to recovery.

TREATMENT

Again, Ormond (1) should be credited for the initial therapeutic observations for the condition under discussion, first published in 1948. At that time he recognized the compressive nature of the ureteral obstructions and the necessity for ureterolysis. The methods of treatment of ureteral compression due to idiopathic non-specific chronic fibrosing retroperitonitis have not been uniform. A summary of the fourteen cases reviewed by us plus our own, reveals the following: in eight of the thirteen successfully treated cases, *bilateral* ureterolysis was performed, four transperitoneally, four extraperitoneally. In two other successfully treated cases only *unilateral* ureterolysis was done, both extraperitoneally. In one, only partially successful case, bilateral transperitoneal ureterolysis was done. In two successful cases, nephrectomy and extraperitoneal ureterolysis of the opposite side were done.

Of the two deaths in the 15 cases, one case had no ureterolysis and died of uremia and was the case in which the autopsy analysis indicated to Ormond (1) the necessity for ureterolysis. In the other fatal case, there had been no ureterolysis but death occurred without uremia and within 24 hours after unilateral nephrostomy, probably of hyperpotassemia. In only one case was the use of simple prolonged (one month) bilateral ureteral indwelling catheters combined with intensive antibiotic therapy successful. In this latter case a two year follow up showed persistence of the mass and moderate unilateral hydronephrosis.

As temporary adjuvant procedures: bilateral nephrostomy was done in four cases; unilateral nephrostomy in four cases; bilateral pyelostomy was done in two cases. One patient required nephrectomy plus nephrostomy on the opposite side. In one case, nephrectomy was required after bilateral nephrostomy. In another case (1), bilateral nephrostomy was the only operative procedure. Thus the outstanding feature of the treatment of the fifteen cases known to us reveals the highly significant figure that 12 out of the 13 successfully treated cases had ureterolysis performed, eight bilaterally, four unilaterally of which two were done after antecedant nephrectomy of the opposite side. The initial control of the

uremia, oliguria or anuria required bilateral indwelling catheters in almost all cases. In nine cases nephrostomies, and in two cases bilateral pyelostomies, were also required for this stage of the disease or as prophylactic measures in relation to ureterolysis. Radiotherapy without ureterolysis was unsuccessful in Ormond's first fatal case (1). It was used successfully in the three cases of Ormond (1) Bradfield (7) and ours as supplements to bilateral ureterolysis. In a case of ureteral stricture with localized periureteral inflammation Oppenheimer, Narins and Simon (6) used radiotherapy with cure after ureteral intubation and lysis had failed.

The outstanding influence of antibiotics in this disease is obvious. It was tried as the primary treatment in the case of Miller, Lipin, Meisel and Long (5). Cortisone therapy was used in our case in the hope of preventing increased or ensuing fibrosis.

AWARENESS OF THE ENTITY

It is of the utmost importance that this entity be brought to the attention of the internist who may obviously see the patient for the first time and to the orthopedist who might have the patient erroneously referred to him, and to the radiotherapist who may be asked to treat an unproven case of suspected retroperitoneal neoplasm with ureteral obstruction.

CONCLUSION

The authors believe that the following be a *modus operandi* in the treatment of the disease once its nature has been recognized:

Emergency relief of the obstruction, i.e. ureteral catheterization or nephrostomy.

Early freeing of the ureters out of the inflammatory mass i.e. ureterolysis.

Radiotherapy only as an adjuvant at most and should not delay early ureterolysis.

Antibiotic and symptomatic supportive therapy.

SUMMARY

A fifteenth case of idiopathic nonspecific fibrosing retroperitonitis causing bilateral ureteral compression is reported. It is imperative that this condition be recognized as a now proven clinical-pathological disease-entity—not only by urologists but by internists, abdominal surgeons, orthopedists and radiotherapists. The successful method of treatment has been outlined, emphasizing the life saving importance of *early* definitive diagnosis by surgical exploration and biopsy and *early ureterolysis*.

ACKNOWLEDGEMENT

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REPLACEMENT OF THE RIGHT RENAL ARTERY BY THE SPLENIC OR INFERIOR MESENTERIC ARTERIES

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Splenorenal arterial anastomosis for the revascularization of the left kidney, and the indications for its clinical application, have recently been reported from this hospital (1). The adequacy of the splenic artery as the source of blood supply to the left kidney had been demonstrated previously by survival experiments in dogs (2); the animals had been subjected to a right nephrectomy and left splenorenal arterial anastomosis. Significant long term survivals were obtained without any appreciable deleterious effect upon the kidney, as examined by intravenous pyelography and following sacrifice. The left splenorenal arterial shunt has also been employed successfully in the human being (1).

It may also be possible to avoid right nephrectomy, in some instances following involvement of the right renal artery by an occlusive process, injury or aneurysm, if a source for a new arterial blood supply can be found. This has been accomplished in the laboratory by anastomosing either the splenic or the inferior mesenteric artery to the divided right renal artery of the dog.

The inferior mesenteric artery in man and the experimental animal is an expendable vessel. Studies by Braithwaite on the rat and the Rhesus monkey indicate that ligation proximal to the last arterial arcade may be performed without danger of ischemia of the terminal large bowel (3, 4). The present experiences in the dog confirm this observation. Inferior mesenteric artery ligation at its origin and preservation of the last arterial arcade is advocated by many in man, in the radical resection of carcinoma of the left colon.

METHOD

The experimental procedure in this study was divided into 3 major groups.

GROUP I

- (a) Spleno-right renal arterial anastomosis;
- (b) Left nephrectomy

Group II

- (a) Inferior mesenteric-right renal arterial anastomosis;
- (b) Left nephrectomy

Group III

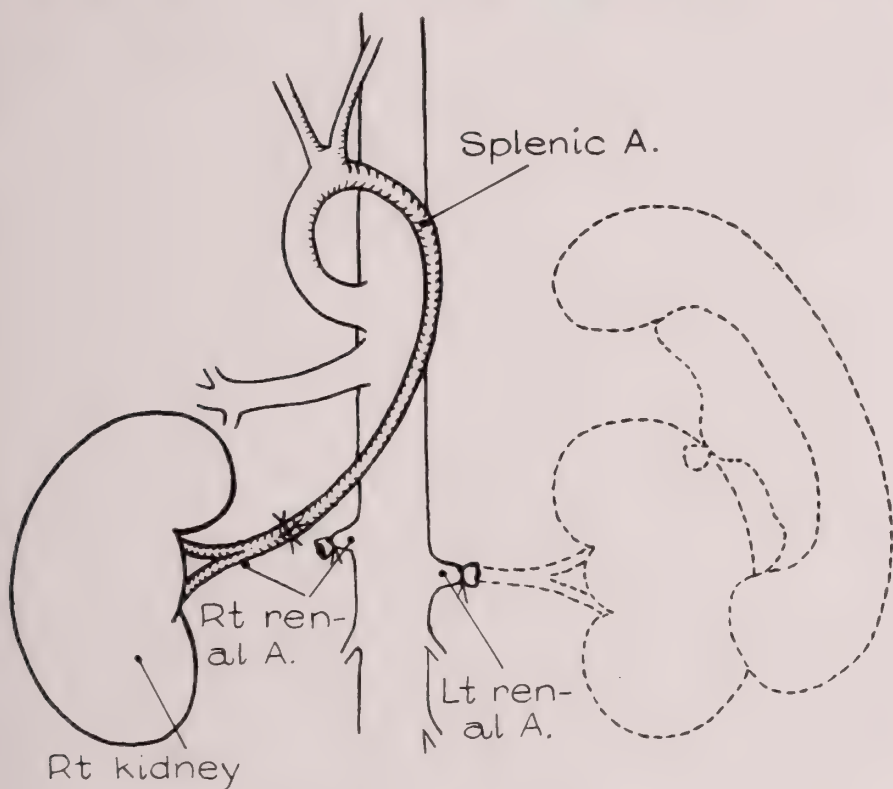
- (a) Autopsy room observations and comparative measurements of the splenic, renal and inferior mesenteric arteries in human cadavers.

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Mongrel dogs weighing from 25 to 75 lbs. were used for groups I and II. All operations were performed under general anesthesia produced by a veterinarian solution of nembutal administered intravenously.

In Group I, a left paramedian muscle-splitting abdominal incision was used. The splenic artery was mobilized from the celiac axis to where it begins to branch close to the hilus of the spleen, ligated distally, clamped proximally with a bulldog clamp and sectioned. The posterior parietal peritoneum over the abdominal aorta was incised and the right renal artery was mobilized, ligated at its origin, clamped distally with a bulldog clamp, and sectioned. The proximal end of the splenic artery was anastomosed to the distal end of the right renal artery with continuous 5-0 silk sutures, interrupted at the lateral angles (2). After the right kidney had been revascularized, a left nephrectomy was performed, making



SPLENO-RENAL ARTERIAL ANASTOMOSIS (RIGHT)

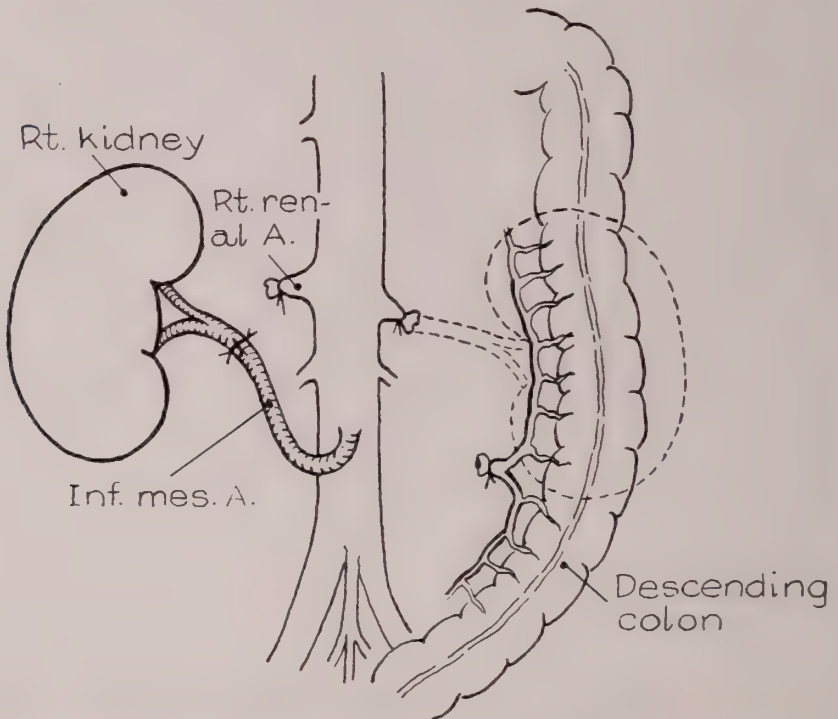
FIG. 1. Spleno-renal arterial anastomosis (right).

survival of the animal entirely dependent upon the spleno-right renal arterial shunt (Fig. 1).

In Group II, a right paramedian muscle-splitting abdominal incision was used. The inferior mesenteric artery was mobilized from the aorta to the marginal artery of the sigmoid colon, ligated proximal to the marginal artery and divided. Hemostasis was achieved by a bull-dog clamp placed proximally on the vessel. The right renal artery was prepared as in Group I, and the proximal end of the inferior mesenteric artery was anastomosed to the distal end of the right renal artery using the same suture technique as in the spleno-right renal arterial anastomosis. A left nephrectomy was then performed (Fig. 2).

Observations and comparative measurements of the splenic, renal and inferior mesenteric arteries in the human cadaver have been made in the autopsy room in order to evaluate their anatomical suitability for the application of the proposed renal revascularization techniques in man.

Special Considerations. The inferior mesenteric artery in the dog was densely encased in perivascular autonomic nerve fibers and ganglia, which were stripped from the vessel during its mobilization. During this dissection the vessel went



INFERIOR MESENTERIC-RENAL ARTERIAL ANASTOMOSIS

FIG. 2. Inferior mesenteric-renal arterial anastomosis.

into marked spasm, reducing its lumen by over fifty per cent. The vasospasm was successfully overcome by the use of two maneuvers. Before dissection of the vessel was started, the perivascular tissue was infiltrated with 1% procaine solution. After the vessel was completely mobilized, it was wrapped in a gauze pledget soaked with papavarine hydrochloric acid solution, while the right renal artery was being prepared for anastomosis.

RESULTS

Seventeen dogs were operated upon, with eight long term survivors. Of the nine dogs that died between one and twenty-two days following surgery, only three died of uremia secondary to thrombosis of the arterial shunt. Intravenous pyelograms performed before sacrifice on all long term survivors were normal. At autopsy, all solitary kidneys with a patent arterial anastomosis were hypertrophied, and otherwise appeared normal both grossly and on microscopic section.

TABLE 1
Right Splenorenal Arterial Anastomosis

Dog	Duration of Right Renal Ischemia (Minutes)	Survival (Days)	Cause of Death	Status of Anastomosis	Intravenous Pyelogram
A33	14	3	Uremia	Occluded	Normal
A34	18	266	Sacrificed	Patent	
A35	22	1	Shock	Patent	
A36	16	247	Sacrificed	Patent	Normal
A37	20	218	Sacrificed	Patent	Normal
A38	52	22	Distemper	Patent	Normal
A39	18	Living			
A40	17	209	Sacrificed	Patent	

TABLE 2
Inferior Mesenteric-Right Renal Arterial Anastomosis

Dog	Duration of Right Renal Ischemia (Minutes)	Survival (Days)	Cause of Death	Status of Anastomosis	Intravenous Pyelogram
IMR1	32	271	Sacrificed	Patent	Normal
IMR2	20	1	Hemorrhage from left renal artery stump	Patent	
IMR3	29	Living			Normal
IMR4	18	5	Uremia	Occluded	
IMR5	35	3	Intussusception & Uremia	Occluded	
IMR6	20	214	Sacrificed	Patent	Normal
IMR7	28	6	Intestinal Obstruction	Patent	
IMR8	25	8	Acute Pancreatitis	Patent	
IMR9	35	10	Pneumonia	Patent	

In each instance when the inferior mesenteric artery had been used, it was about twice as large in the long term survivors as it had been originally. The detailed data are presented in Tables 1 and 2.

According to autopsy room observations of the splenic, renal and inferior mesenteric arteries in the human, the splenic and inferior mesenteric arteries are anatomically suitable for renal arterial anastomosis. Following the mobilization of these vessels, the splenic and inferior mesenteric arteries are long enough to reach either renal artery with ease and without tension. The calibre of the vessels is sufficiently comparable to permit a satisfactory anastomosis. Actually, the observations indicate that the splenic and inferior mesenteric arteries are anatomically even more suitable for renal revascularization in the human than in the dog.

DISCUSSION

There are a number of clinical conditions where the above described techniques of renal revascularization may be employed to avoid nephrectomy or loss of renal function. Whereas the spleno-left renal arterial anastomosis has been employed clinically by us, the right renal revascularization methods have not been performed in the human to date. Spleno-left renal arterial anastomosis in the management of a case of aortic thrombosis (Leriche's syndrome) was successfully performed on April 19, 1955 (1). The patient was a 44 year old man with thrombosis of the terminal aorta. Resection of the occluded segment and replacement by a preserved aortic bifurcation homograft had been performed three months previously. Because of inadequate run-off into the iliac and femoral vessels, the graft thrombosed, and the occlusive process was demonstrated by aortogram to extend proximally to the level of the origin of the renal arteries. A spleno-left renal arterial anastomosis was constructed, in order to provide a more secure blood supply to at least one kidney, should the aortic thrombosis ascend to include the origins of the renal arteries. Intravenous pyelograms performed 2, 3, 5, 10, and 14 months postoperatively revealed visualization of both kidneys, with the left side visualizing better than the right at each study. The blood urea nitrogen level has remained within normal limits. The patient is in excellent condition 24 months after the vascular anastomosis. Differential renal function studies indicate that the left kidney has a greater function than the right; these will be reported in detail subsequently.

The employment of spleno-left renal arterial anastomosis to avoid renal ischemia during resection of aneurysms involving the renal artery bearing portion of the aorta has been reported from this laboratory (5). In this experimental study the right kidney was revascularized either by implanting the right renal artery into the aorta proximal to the resected portion, or into the graft. The inferior mesenteric artery is usually not available as a source for right renal revascularization in the management of abdominal aortic thrombosis or aneurysm. However, in cases with a solitary functioning kidney, whether it be in the pelvis or on the right side, the splenic artery may be used as a source of new blood supply.

Renal artery disease may cause hypertension because of partial impairment of kidney blood supply by the Goldblatt phenomenon (6). Embolism, thrombosis, fibrous intimal proliferation, aneurysm, arteriosclerotic plaques, and syphilitic arteritis are the lesions, according to Poutasse, (7) which may produce this type of hypertensive disease. Nephrectomy results in a prompt fall in blood pressure to normal in patients with hypertension of brief duration due to one of these obstructing renal artery lesions. Translumbar aortography is the most effective method of demonstrating the presence of renal artery pathology, and is an essential part of the diagnostic armamentarium when these specific lesions are suspected. In many instances, nephrectomy can be avoided by renal revascularization procedures. Poutasse et al. reported a case of bilateral stenosis of the renal arteries, with hypertension due to fibrous intimal proliferation, treated successfully by replacement of the stenosed proximal segments of the renal arteries by arterial homografts (8). The construction of a spleno-left renal and an inferior mesenteric-right renal arterial anastomosis in this type of case would achieve a similar result, without the use of preserved homografts, utilizing the advantages of fresh autografts.

The sacrifice of a kidney with an extrarenal aneurysm of the renal artery is no longer the procedure of choice for the management of this lesion. The aneurysm can be resected and the kidney blood supply re-established by a spleno-renal or inferior mesenteric-renal arterial anastomosis. Theoretically, it is now possible to save a kidney with an aneurysm arising from the bifurcation of the renal artery by anastomosing the splenic and inferior mesenteric arteries to each major branch of the renal artery after the aneurysm has been resected. Two cases of bilateral renal artery aneurysms have been reported in the literature, (9, 10) and therapy may now be feasible in such instances.

Either of these arterial anastomoses may be employed when faced with an acute operative injury to a renal artery and the kidney saved. Kidney salvage is possible in the management of renal pedicle trauma in either military or civilian accidents, provided prompt therapy can be instituted before irreversible renal ischemia has occurred. The maximum safe period of renal artery occlusion in man is not known, but Ellis has reported a case wherein the right renal artery was occluded for 135 minutes with preservation of renal function (11).

An anomalous renal artery may cause obstruction at the ureteropelvic junction with hydronephrosis. When the vessel is large, fear of infarction of a significant portion of the kidney has resulted in the development of complicated ureteropelvic reconstructive procedures. Instead, the obstructing vascular band may be divided, and the splenic or inferior mesenteric artery anastomosed to the distal end of the anomalous vessel.

SUMMARY

1. The splenic and inferior mesenteric arteries were used to replace the right renal artery in dogs.
2. The inferior mesenteric artery in man and the experimental animal is an expendable vessel.

3. Clinical application of these techniques is suggested in the management of a number of disease processes involving the right renal artery.

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NEUROENDOCRINE SYSTEM AND OBESITY

STUDIES IN "YELLOW" MICE*

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Mice of strain YBR Wi seem particularly suited for studies of obesity. This strain is made up of about even numbers of grey and yellow coated individuals, although within any litter the distribution of yellows and greys may vary. The yellows carry a gene A^y which the greys do not possess. If fed enriched diets, the yellows become obese, while the greys do not. In accordance with the tendency to obesity, the yellows have a higher food consumption and better food utilization than the greys. Except for coat color and potential obesity greys and yellows are similar in their anatomic and physiologic constitution as well as in their proneness to develop such conditions as xerophthalmia, osteoarthritis, aortitis, pyelonephritis, amyloidosis, hyperglycemia, and hyperplasia of the pancreatic islets. Endocrine imbalances possibly associated with disturbances in the metabolism of vitamin A seem to exist in both genotypes, although no major structural differences were observed in the endocrine glands including the hypophysis (1-7). The possibility that dysfunction of the hypothalamus with or without associated morphological changes might be the cause of metabolic differences between greys and yellows has so far not been investigated. In the search for such cerebral lesions the brains of YBR mice were studied. Some differences in brain structure were found to be associated with differences in coat color and are herewith reported.

MATERIAL AND METHODS

The mice were raised in our laboratory and were kept on a stock diet of Purina laboratory chow or on diets enriched with lard or cornstarch. Food and water were available at all times. Differences in diet did not influence the findings in the brain and will therefore be disregarded hereafter. The brains of 112 grey- and 83 yellow coated males and females 6 to 23 months old at the time of death were available, but since the findings were consistent, the brains of only 41 greys and 45 yellows were examined systematically.

At necropsy the brains were removed as a whole and usually fixed in 10 per cent formalin or Bouin's solution. For special stains the material was placed in

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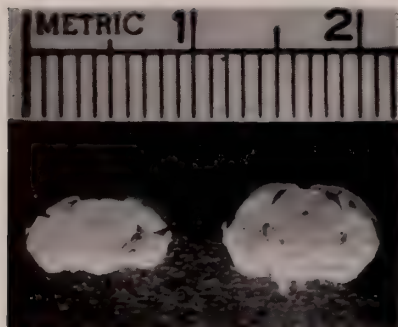


FIG. 1

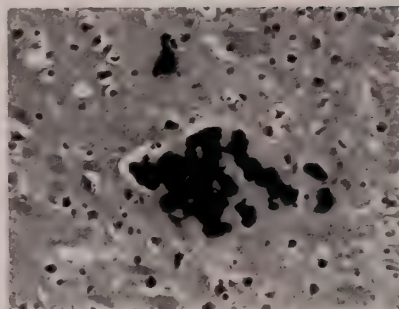


FIG. 2

FIG. 1. Coronal sections through the brains of a yellow coated (left) and grey coated (right) male mouse 18 months of age made at the level of the infundibulum. The brain of the yellow is distinctly smaller than that of the grey mouse.

FIG. 2. Calcified plaque in the thalamus of a yellow coated mouse. 190 \times .

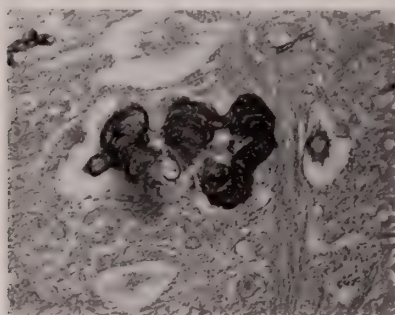


FIG. 3

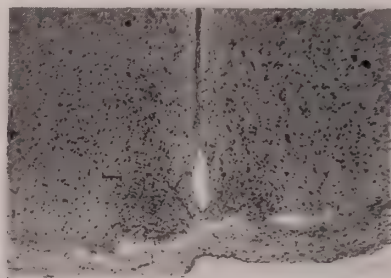


FIG. 4

FIG. 3. PAS stain of a calcified plaque. 315 \times .

FIG. 4. Paraventricular nuclei of a grey coated mouse. 40 \times .

silver nitrate, absolute alcohol, Weigert's neuroglia or myelin mordants. Routinely the tissues were embedded in paraffin; frozen sections were made if needed for a special stain. In a number of cases the thalamic, subthalamic and hypothalamic regions were cut serially in order to permit quantitative studies in particular of the paraventricular nuclei. Sections were stained with hematoxylin and eosin, Sudan IV, PAS, or Gomori trichrome; in addition, stains for Nissl substance, myelin sheaths, neuroglia, axons and neurofibrils were carried out.

OBSERVATIONS

Data on the visceral lesions occurring in these mice, on life span and weights have been reported elsewhere (2, 3).

Gross findings: The brains of yellows were smaller than those of greys of the same sex and age, and also smaller than those of C57BL or A mice. This difference was noted in both length and width, and affected particularly the thalamus, hypothalamus, and cerebellum (Fig. 1). Occasionally hydrocephalus was seen in mice of either coat color.

Microscopic findings: In random sections the brains of yellows showed deposits

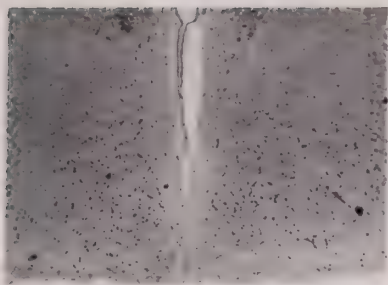


FIG. 5

FIG. 5. Paraventricular nuclei of a yellow coated mouse sectioned at the same level as those shown in figure 4. Decreased cellularity as compared to corresponding nuclei in grey coated animal. 40 \times .

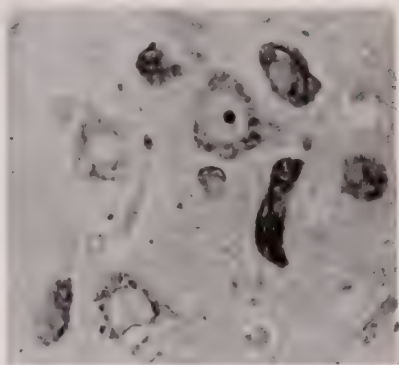


FIG. 6

FIG. 6. Nissl stain of thalamus of a yellow coated mouse. Swelling, vacuolation, and homogenization of cytoplasm with loss of Nissl substance and dissolution of nuclei in some, and pyknosis in other nerve cells. 460 \times .

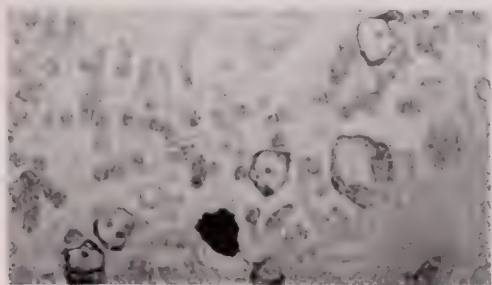


FIG. 7. Nissl stain of cerebellum of a yellow coated mouse showing regressive changes in Purkinje cells similar to those shown in figure 6. 478 \times .

of calcium deeply stained with hematoxylin and forming irregular masses or small bodies (Fig. 2). Calcified plaques were usually located in thalamus and hypothalamus in close approximation to and around small blood vessels. Here and there, nerve cells had undergone calcification. With special stains, PAS positive and lipoid material was found in association with the precipitated calcium (Fig. 3). In yellows, these lesions were regularly present at 15 months of age, but they occurred earlier than that. In greys, deposits were found only in old age. The ratio of yellows to greys showing these plaques was about 18:1.

In coronal sections, there was a decrease in the number of nerve cells in the paraventricular nuclei of yellows as compared to those of greys (Figs. 4, 5). In yellows, the nerve cells present were small and widely spaced. In greys, the thickness of the paraventricular nuclei as estimated from the number of serial sections obtained varied from 200 to 250 μ ; in yellows, it rarely exceeded 50 to 60 μ .

Regressive changes were noted in the nerve cells of the thalamus, hypothalamus and the cerebellum of yellow coated animals. The degenerating cells were markedly enlarged; frequently the nuclei were pushed towards the periphery of

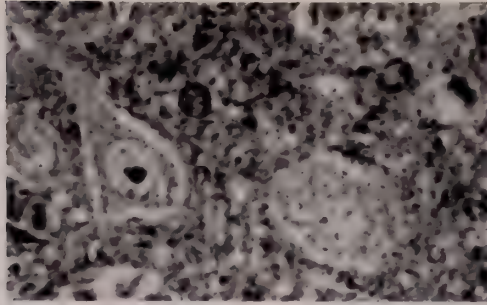


FIG. 8. Degenerated nerve cells of thalamus of a yellow coated mouse containing myelin positive material 855 \times .

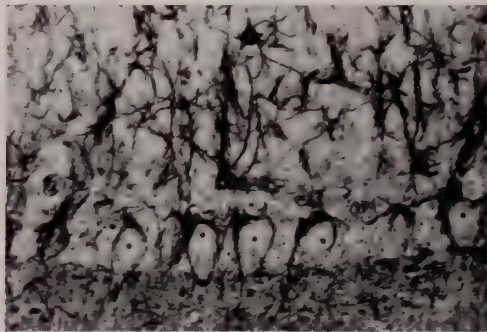


FIG. 9. Silver impregnation of cerebellum of a grey coated mouse showing well preserved Purkinje cells and fibrillar network. 310 \times .

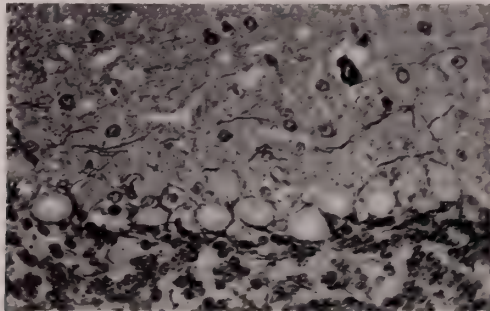


FIG. 10. Silver impregnation of cerebellum of a yellow coated mouse. Degenerating Purkinje cells and loss of fibers. 310 \times .

the cells and showed pyknosis or karyorrhexis. There was cytoplasmic vacuolation or homogenization with disarrangement or lysis of the Nissl substance and deposition of slightly sudanophilic, and PAS or myelin positive material (Figs. 6-8).

Silver impregnations (Figs. 9-11) disclosed a marked loss and break-up of fibrils about degenerating nerve cells, and adjacent glial fibrils appeared closely knit. However, diffuse foci of gliosis were not found in the many sections studied. Glial reaction was slight at best; occasionally satellitosis was suggested in the vicinity of injured nerve cells.

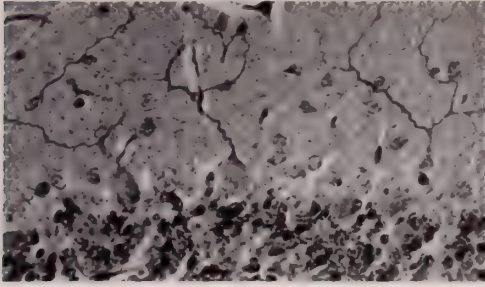


FIG. 11. Nissl stain of cerebellum of a yellow coated mouse. The cytoplasmic processes are elongated, branched, and clubbed. 335 \times .

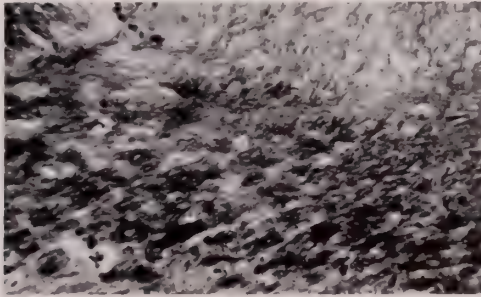


FIG. 12. Myelin sheath stain of subthalamic region of a yellow coated mouse. White flecks indicate foci of demyelination. 175 \times .

There were small foci of demyelination particularly in the thalamic and cerebellar hypothalamic pathways (Fig. 12).

DISCUSSION

Examination of the brains of yellow- or grey-coated mice of strain YBR/Wi disclosed structural variations which constitute a major difference between the otherwise phenotypically similar genotypes. The brains of the yellows, especially the paraventricular nuclei, hypothalamus and cerebellum were smaller than those of the greys. Microscopically, there was decrease in the number of nerve cells and widespread degeneration of neurons with formation of calcified plaques in the involved areas.

Two main questions arise in connection with these observations: What is the nature of the morphological findings, and do these structural changes constitute the basis for the metabolic disorder present in the yellow- and absent in the grey-coated mice?

The morphological changes are twofold: (a) hypoplasia of the paraventricular nuclei, and (b) degeneration in thalamus, hypothalamus and cerebellum.

The structure of the paraventricular nuclei was already found to be altered in mice six months of age, and may have been present earlier than that. However, our studies do not allow definite conclusions regarding this point. These changes remained fairly stationary through life; they may be primary, possibly congenital and genetically determined, but they may conceivably be secondary to another disorder. It has recently been shown with the aid of injection techniques that the

paraventricular nuclei, the hypothalamus and cerebellum are closely linked owing to a common vascular supply, and that the cells of the paraventricular nuclei may undergo degeneration owing to changes in blood chemistry such as anoxia. These changes are easily produced and reversible (8). Regardless of whether the hypoplasia of the paraventricular nuclei is congenital or acquired during life, it might constitute the morphological substratum for the tendency to obesity of the yellow coated individuals. Hypothalamic dysfunction is related to certain types of adiposity, and obesity was produced in mice whose paraventricular nuclei were damaged by injections of goldthioglucose (9). The problem remains, however, why the yellows become obese only, when fed enriched diets, even though the cerebral lesions are present irrespective of the diet consumed. Since both high carbohydrate and high fat diets will produce adiposity, it seems doubtful that a disturbance of glucostatic mechanisms alone could be responsible for this condition. That a serious disequilibrium of carbohydrate metabolism is however present in these mice, is indicated by the frequent occurrence of high blood sugar levels and hypertrophic pancreatic islets particularly after consumption of a carbohydrate enriched diet (3).

The calcified plaques which were common in yellow coated individuals are histochemically not unlike those observed in the globus pallidus of non-arteriosclerotic humans suffering from a variety of disorders (10). Moreover, some of the cellular changes noted in the yellows bear resemblance to those seen in amaurotic idiocy.

In contrast to the paraventricular lesions, calcified plaques as well as degeneration of neurons increased with advancing age. The latter were absent in young animals, and may therefore represent the result of an abiotrophy. However, they may also be non-genetic in origin and secondary to either the hypothalamic changes or to metabolic disturbances such as vitamin A deficiency present in these mice (3). Although the mode of action of vitamin A deficiency on the nervous tissues has been interpreted in different ways by different investigators (11, 12), there is little doubt about the existence of such an effect. However, since both grey- and yellow-coated individuals are prone to develop vitamin A deficiency, one would have to postulate an increased sensitivity of the yellows to the deficiency. This would in turn point to a genetic origin of the condition. Further studies in "yellow" mice may help to elucidate some of the still unsolved problems of hypothalamic function and dysfunction which are not adequately understood at the present time.

SUMMARY

Yellow coated mice of strain YBR/Wi show hypoplasia of the brain, and specifically of the paraventricular nuclei associated with regressive changes in the neurons of thalamus, hypothalamus and cerebellum. These lesions which were not conspicuous in grey coated individuals are thought to be related to the tendency of yellows to develop obesity.

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HYPERTHYROIDISM AND MYASTHENIA GRAVIS

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The association of various disorders of neuro-muscular function with hyperthyroidism has been noted for many years. Such observations were recorded in the last century but many of the cases are difficult to classify because the diagnostic criteria available to the early clinicians were not as specific as those presently employed. A critical review of some of the early reports cited by Sattler (1) as examples of neuro-muscular dysfunction in hyperthyroidism often leaves one uncertain of the nature of the neurological process and, in fact, of the presence of hyperthyroidism.

The following neuro-muscular disturbances are associated with thyroid overactivity:

1. Exophthalmic ophthalmoplegia.
2. Acute thyrotoxic encephalo-myopathy.
3. Acute and chronic thyrotoxic myopathy.
4. Periodic paralysis.
5. Myasthenia gravis.

1. *Exophthalmic Ophthalmoplegia.* Weakness of the external ocular muscles and convergence defects are frequent in Graves' disease but the severe forms with complete fixation of the globe are relatively rare. The muscles of upward gaze are most frequently involved. The ocular manifestations may be unilateral or bilateral and bear no direct relation to the clinical severity of the hyperthyroidism. They may precede the onset of the hyperthyroid state and may even appear after the active phase of hyperthyroidism has disappeared, either spontaneously or as a result of treatment. The ophthalmoplegia is usually associated with proptosis and chemosis and occasionally with ptosis. The syndrome of "pretibial myxedema" is sometimes seen.

2. *Acute Thyrotoxic Encephalo-myopathy.* This disorder has been described by Waldenstrom (2). He reported 10 cases characterized by coma, bulbar signs, muscle paresis and extreme exhaustion. It is not clear whether these patients represent a distinct clinical entity or are examples of severe exacerbations of the hyperthyroid state as seen in thyroid storms. Waldenstrom saw good results following large doses of iodine.

3. *Acute and Chronic Thyrotoxic Myopathy.* Muscle weakness and some degree of muscle wasting is so common in hypothyroidism that it can scarcely be considered a complication of the disease. It is only when the myasthenic symptoms dominate the clinical picture that a special delineation is justified. Classical

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hyperthyroid symptoms may be absent. The muscle atrophy in Graves' disease was first reported by Bathurst (3) in 1895. Charcot (4) described "l'effondrement des jambes" in 1889 and the syndrome is also known as "giving way of the legs." In the early stages the attacks are transient and recovery is complete but as the disease progresses paraparesis and paraplegias may result. Bulbar signs are rare. The deep reflexes are depressed and sensory changes are not present. Marked tremulousness of the knees is frequently present and severe muscle wasting is seen. The lower extremities are more commonly and more severely involved than the upper. The proximal muscle groups are affected predominantly and atrophy of the shoulder girdles may be extreme. Improvement occurs as the hyperthyroid state is controlled.

4. *Periodic Paralysis*. Talbot (5) reviewed some 400 cases of periodic paralysis in 1941. The ratio of males to females was 3-1, in contrast to hyperthyroidism where the ratio is 1 male to about 4 females. Most of the females affected by periodic paralysis have hyperthyroidism while males are usually euthyroid. The attacks are associated with a lowered concentration of potassium in the serum without increased potassium excretion in the urine. Conn (6) has recently suggested that increased aldosterone secretion may be a factor in precipitating attacks of paralysis when periodic paralysis is associated with hyperthyroidism. Control of the hyperthyroid state reduces or abolishes the paralytic episodes.

5. *Myasthenia Gravis and Hyperthyroidism*. Most of the reported instances of the clinical association of Myasthenia Gravis and Hyperthyroidism were made before modern methods for the delineation of the two diseases were available. In 1908 Rennie (7) recorded an example of this association and further reports were made by Cohen and King (8), Bartels and Kingsley (9), Levy, Meadows and Gunnar (10), Scwab and Chapman (11), Thorner (12), McEachern and Parnell (13). Cohen and King commented on the similarities between the two diseases. They pointed out that hypertrophy of lymphoid tissue, lymphocytosis occasional glycosuria and lymphorrhages in muscle tissue are found in both conditions. Thorner and McEachern and Parnell were impressed by their observations that there seemed to be an inverse relationship between the two diseases. They saw aggravation of the myasthenia gravis as the hyperthyroidism was controlled and remission of the myasthenia when the Graves' disease was uncontrolled. More recently Maclean (14) has confirmed these observations. Others are not convinced that this "see-saw" relationship is frequent.

Millikan and Haines (15) reported 25 cases of the association of these two diseases. One of these responded to 1/180 of the normal dose of curare required for curarization while patients with uncomplicated Graves' disease respond normally to curare and to the cholinergic drugs (16). In this series the following time relation between the two diseases were noted:

	Cases	Percent
Graves' disease first	9	36
Myasthenia Gravis first	8	32
Simultaneous	2	8
Simultaneous (?)	3	12
Graves' first but more than 5 years apart	3	12

Millikan and Haines suggest that about 5 percent of all cases of myasthenia gravis have Graves' disease at some time of their illness but that only a "fraction of 1 percent" of hyperthyroids have myasthenia gravis. They saw no instances of the "see-saw" previously mentioned. An index of the severity of the problem when both of these diseases occur in the same patient is the fact that 10 of the 25 patients in this series died.

Present Study: Patients were selected from the Myasthenia Gravis Clinic of The Mount Sinai Hospital and in each instance an unequivocal diagnosis of myasthenia gravis had been established. They were then studied as to their thyroid function by the following techniques:

1. The 24 hour thyroidal uptake of I-131 after a tracer dose; Normally less than 55%.

2. The plasma levels (17) of protein-bound I-131 at 72 hours after the tracer dose (PBI-131); Normally less than 0.26% of the administered dose per litre.

3. The plasma (or serum) protein-bound iodine level (PBI) (18); Normally 3.5-7.5 micrograms per 100 ml.

The results of these studies are presented in the table I.

Case Reports. We are here reporting in abstract form the data on the three patients that we observed who had both hyperthyroidism and myasthenia gravis while under our observation.

Case 1. At the age of 14, in 1946, this white woman developed classical hyperthyroidism with a basal metabolic rate of plus 78 percent. She was temporarily controlled by propylthiouracil and iodine. Her disease reactivated in 1949 and an attempted thyroidectomy had to be abandoned because of the patient's poor condition on the operating table. In 1951 she received I-131 at another institution with an apparent control of her hyperthyroidism. In December 1953 she developed symptoms of myasthenia gravis with marked bulbar symptoms. She was first seen by us in April 1954 when she presented classical symptoms of both myasthenia gravis and hyperthyroidism. The uptake of I-131 was 80 percent of the tracer dose and the plasma levels of PBI-131 at 72 hours was 0.56 percent of the administered dose per litre. The PBI was 9.8 micrograms per 100 ml. of serum. On April 22, 1954 she was given a therapeutic dose of 2.0 mc of I-131 followed by Lugol's solution. She did well until May 10, 1954 when her myasthenic state deteriorated rapidly. She developed a severe myasthenic crisis and died on June 3, 1954 in spite of the use of the respirator, tracheostomy and antibiotics. Post-mortem examination revealed a severe hemorrhagic tracheo-bronchitis and pneumonia. The thyroid was atrophic.

Case 2. In this 34 year old negress symptoms of hyperthyroidism and myasthenia gravis developed almost simultaneously in 1951. She was treated with propylthiouracil until 1953 and the myasthenia was fairly well controlled with cholinergic drugs. In October 1953 studies of thyroid function revealed an uptake of 78 percent of the tracer dose, a PBI-131 level of 0.26 percent of the administered dose per litre of plasma and protein-bound stable serum iodine of 12.2 micrograms per 100 ml. She was treated on October 19, 1953 with 4.0 mc of I-131.

TABLE I
Euthyroid Subjects

Case #	I-131 Uptake	PBI-131	PBI
1	33	0.07	
2	19	—	4.6
3	27	—	
4	36	0.10	
5	60	0.16	4.4
6	32	0.08	
7	39	0.05	
8	50	0.09	
9	35	0.10	
10	48	0.09	
11	60	0.09	3.6
12	32	0.09	
13	37	0.03	
14	50	0.18	
15	42	0.10	4.8
16	43	0.36	
17	55	0.20	
18	22	0.08	
19	39	0.18	
20	27	—	
21	38	0.05	
22	48	0.20	
23	42	0.09	
24	40	0.05	
25	28	0.15	4.4
26	28	0.05	
27	28	0.03	
28	27	0.10	
29	19	—	
30	28	0.04	5.3
31	33	0.07	
32	40	—	
33	34	0.05	4.8
34	28	0.10	
35	42	0.08	
36	45	0.07	
37	62	0.09	5.3
38	28	—	
39	20	0.01	
40	35	—	
41	60	0.15	7.1
42	27	—	
43	28	—	6.1
44	36	0.16	
45	60	0.19	5.9
46	21	0.20	
47	32	—	
48	—	0.05	

TABLE I—*Continued*

Case #	I-131 Uptake	PBI-131	PBI
49	45	0.08	
50	20	—	
51	65	0.22	
52	40	0.09	
<i>Hyperthyroid Subjects</i>			
1	80	0.56	9.8
2	78	0.26	12.2
3	60	0.35	—
Total cases of myasthenia gravis studied.....			55
Total found euthyroid.....			52
Total found hyperthyroid.....			3

She was doing well under our care. In January 1954 she developed a pulmonary infection and was taken to another hospital where they were not informed of her myasthenia gravis. No cholinergic drugs were administered and the patient deteriorated rapidly and died in a few days. No post-mortem was obtained. At the time of death her hyperthyroidism seemed under good clinical control.

Case 3. This white woman developed classical myasthenia gravis at 35 years of age in February 1954 and came under our observation soon thereafter. As the problem of hyperthyroidism associated with myasthenia gravis was under serious investigation at the time and because of the presence of some exophthalmos, studies of thyroid function were performed and revealed an I-131 uptake of 60 percent, PBI-131 levels of 0.35 percent and a PBI of 17.5 micrograms. She was treated with 2.7 mc of I-131 on March 22, 1954. This was apparently sufficient to cure her hyperthyroidism. Her uptake was 28 percent on June 7, 1954 and 40% on October 4, 1954. Her myasthenia was difficult to control and she suffered from several cholinergic crises. On several occasions she required respirator care and she died on April 7, 1955 from a severe infection of her respiratory tract.

In addition to the three case reports detailed above in which we were able to observe and confirm the simultaneous presence of myasthenia gravis and hyperthyroidism, we were able to find in our series of 282 cases of myasthenia gravis 6 additional patients who probably had hyperthyroidism before they came under our care. One of these developed myasthenia gravis in 1925 and had a subtotal thyroidectomy for hyperthyroidism in 1932. She was alive in 1953. Another manifested both diseases simultaneously in 1945. She was operated upon and was alive in 1957. A third patient was operated for hyperthyroidism in 1925, developed myasthenia gravis in 1930 and was alive in 1937. The fourth had a thyroidectomy for hyperthyroidism at the age of 16 and developed myasthenia gravis at 21. She is still alive at the age of 23. The fifth case of myasthenia gravis had less clear symptoms of hyperthyroidism but seemed to improve on antithyroid drugs. He is still alive. The sixth patient was a girl who had a thyroidectomy for Graves' at 16, developed myasthenia gravis at 18 and is alive at 23.

Five patients were operated upon for non-toxic nodular goitre before the appearance of myasthenia gravis and one patient had a thyroid carcinoma.

Mortality. In 282 patients with myasthenia gravis followed for a period of from 1 to 15 years, 43 deaths occurred of which 37 were directly related to the basic disease, a mortality of 13%. All three patients with myasthenia gravis in whom we could establish an unequivocal diagnosis of hyperthyroidism while under our observation died. There were 6 patients who may have had an active phase of hyperthyroidism before they came under our care. Four of these were cured of their hyperthyroidism before they developed myasthenia gravis, one developed both diseases simultaneously and survived after thyroid surgery and the sixth is under control with antithyroid drugs. The problem of a see-saw relation between the two diseases remains unsettled, but our cases 1 and 3 may add some support to this concept.

SUMMARY

In a series of 282 patients with myasthenia gravis followed by one of us (K. E. O.) for a period of from 1 to 15 years we were able to establish the presence of active hyperthyroidism in three. All three of these patients died. In one of them a euthyroid state had been restored by the use of I-131.

The presence of hyperthyroidism in the course of myasthenia gravis is of serious prognostic significance and greatly increases the mortality from the disease.

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GAUCHER'S DISEASE, PRESENTING AS WIDESPREAD RESORPTION OF BONE

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The diagnosis of Gaucher's disease must always be suspected in a patient with a large liver and a very large spleen, especially when the slowly increasing enormous size of liver and spleen contrasts with a satisfactory general condition. The liver function tests are nearly always normal. In this disease the external lymphnodes are not enlarged, but the invisible lymphnodes of mediastinum and abdomen often harbor nests of Gaucher cells, i.e. swollen reticulum cells loaded with an abnormal lipoid, kersasin. Gaucher cells also proliferate in the bone marrow and sometimes in the microglia of the posterior lobe of the pituitary (1). Such signs of hypersplenism as anemia, leukopenia and thrombopenia are often present. Hemorrhagic tendency is a rather frequent occurrence. Other well known signs are the brownish pingueculae of the conjunctivae and the leaden or brown pigmentation of the skin which is sometimes most marked at the legs (2, 3).

The proliferation of Gaucher cells in the bone marrow gives rise to characteristic deformations of the skeleton. Gradually it has been realized that the correct diagnosis of Gaucher's disease can often be suspected after the inspection of the roentgenograms of the bones. The proliferating Gaucher cells destroy the trabecular structure of the cancellous bone from which a moth-eaten appearance of the involved skeletal part ensues. The cortex of the bone is also thinned and even eroded by the onslaught of the Gaucher cells. In the later stages of the disease partial sclerosis of the Gaucher lesions is sometimes present. Formation of new bone may take place within the medullary cavity of the Gaucher bone, due to a secondary calcification of collagenous fibers in old Gaucher lesions. In such cases the affected bones present a mottled, moth-eaten appearance on the roentgenograms. Periostitis hardly ever occurs, nor is the articular cartilage invaded by Gaucher cells. In the older age groups, non-specific osteoarthritic changes complicate the Gaucher degeneration of the bones.

Aching of the bones may occur, and spontaneous fractures have been described. In exceptional cases, the swelling and tenderness of the diseased bones are a major complaint, and may present as rheumatic manifestations. In rare instances, these signs have been so acute that osteomyelitis was erroneously diagnosed.

The proliferation of the kersasin-laden histiocytes often causes an increase of the diameter of the bone. This swelling of the bone is most marked in the distal part of the femur. The "waistline" of the lower femur disappears and a bottle

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or club shaped deformity of the metaphyseal area results. The latter anomaly is usually referred to as an "Erlenmeyer flask appearance" of the femur (4).

The same proliferation of Gaucher cells may debilitate the neck of the femur. As a secondary effect, aseptic or avascular necrosis, allegedly due to embolization of blood vessels by Gaucher cells, results. This, under influence of mechanical stresses and weight bearing, leads to partial collapse of the femur neck and resorption of the acetabular bone. Ultimately, the x-ray picture of the deformity of the femoral head may resemble a severe form of osteoarthritis.

In younger persons the avascular necrosis leads to bilateral coxa vara, mushrooming of the femur heads and widening and shortening of the femoral necks. In such patients Gaucher's disease presents as Legg-Perthes' disease or osteochondritis juvenilis deformans. There is, however, one difference: in Legg-Perthes' disease the epiphyseal growth nucleus is normal before the osteochondritis begins. In Gaucher's disease—as far as is known—the epiphyseal center is never completely normal (5). Comparable lesions are sometimes present in the neck and the head of the humerus, in the pelvis and in the spine. Gaucher patients with widening of the lumbar intervertebral disks and partial collapse of the vertebrae have occasionally been observed. In other cases, the vertebral lesions have resulted in gibbus formation and erroneous diagnoses of tuberculosis have been recorded. The latter error can usually be avoided, because in tuberculosis the intervertebral disk is destroyed, whereas in Gaucher's disease the disk remains intact.

Thanks to these well known clinical and radiological points, the diagnosis of Gaucher's disease usually does not offer too many difficulties. The ultimate confirmation of the diagnosis is obtained by bone marrow puncture. On the other hand, cases of Gaucher's disease exist where all the popular clinical signs and the "typical" roentgen anomalies of the skeleton are absent except for an apparently insignificant mild chronic anemia.

Here follows the observation of a middle-aged woman with Gaucher's disease in whom neither hepatosplenomegaly nor anemia could be elicited. Previous to admission the radiological examination of the spine had led to the diagnosis of postmenopausal osteoporosis. Careful examination soon indicated that the localization of the resorption of bone excluded the possibility of postmenopausal osteoporosis. The diagnosis remained completely unclear until a bone marrow puncture revealed the presence of Gaucher's disease.

CASE REPORT

This 65 year old female patient was admitted to the Beth-El Hospital in November 1956 with the chief complaint of back pains. Fifteen years previously she had begun to suffer from mild paroxysms of dorsal back pain. These pains occasionally radiated in a vise or girdle-like fashion around the chest and the upper abdomen. Initially, the pain attacks lasted for five or ten minutes. In later years, however, the pains became progressively more severe and the attacks more frequent. By the end of 1954 the attacks were occurring daily. In February 1955, while walking downstairs, she developed such a severe paroxysm of back pain that she was hospitalized elsewhere. X-rays were made and fractures of two vertebrae were found. The patient received ten x-ray treatments which improved the pain. However, two months later the pains recurred and disappeared only after she

started wearing a brace, which extended from the shoulders to below the hips. In this way she was able, for about eight months, to walk without significant pain.

She was relatively well until August 1956 when suddenly without precipitating cause, the back pain recurred. Again the pains radiated to the flanks, especially to the left side. At admission she complained of constant back pain with frequent acute spasms of pain during which she "cramped together". She had no muscle weakness, numbness or tingling sensations in the extremities. In the course of years she had noticed that her body length had decreased and that her back had become rounded. Lately she had noticed shortness of breath during walking. These attacks were immediately relieved by rest. She had no edema, paroxysmal nocturnal dyspnea, cough or anginal pains. There was no loss of weight. No complaints referable to other organ systems were registered. In January 1953 a vaginal hysterectomy had been performed for a prolapse of the uterus.

Physical Examination revealed a well built, normally nourished middle-aged woman who was not in acute distress. She could only get up from a chair with difficulty, walked slowly and painfully; she could hardly turn around in bed because of pains in the back. The patient had a light brown, somewhat sallow, skin color which she claimed was a life-long characteristic. There were no enlarged lymphnodes. The eyes, ears, nose and throat were normal. No typical pingueculae were present. The dorsal part of the vertebral spine showed a rounded kyphosis. The chest was emphysematous. Percussion and auscultation of the thorax did not reveal any abnormalities except for decreased breath sounds. The heart was enlarged to the left. The heart border reached two finger breadths to the left of the medial clavicular line. The point of maximal impulse was in the sixth intercostal space. There was a grade two to three apical systolic murmur. The second aortic sound was louder than the second pulmonic sound. The abdomen was slightly tender on pressure of both upper quadrants. Liver, spleen and kidneys were not palpable. Traube's space was tympanitic. The extremities were normal, the deep reflexes and the abdominal reflexes were active. There were no pyramidal reflexes. No edema. Rectally and vaginally there were no abnormalities except for the absence of the corpus uteri.

Laboratory Data: Urinalysis revealed the specific gravity to be 1.020 and protein and glucose were normal. Microscopically a few leukocytes were present. Hemoglobin, 12.5 grams per cent; red blood cells, 4,900,000 per cu. mm.; white blood cells, 5,100 per cu. mm. with 4 staffs, 70 per cent segmented, 1 per cent eosinophiles, 20 per cent lymphocytes and 5 per cent monocytes; reticulocytes, 0.6 per cent; platelets, 145,000 per cu. mm.; hematocrit, 43 per cent; sedimentation rate, 18 mm per hour (Westergren); bleeding time, 3 minutes; coagulation time, 2½ minutes; prothrombin time, 70 per cent of normal; fasting blood sugar, 103 mg grams per cent; blood urea nitrogen, 19 mg per cent; creatinine, 1.4 mg per cent; total protein, 6.2 per cent; serum albumin, 4.7 grams per cent, serum globulin, 1.5 grams per cent; alkaline phosphatase, 5.8 King Armstrong units; cephalin flocculation, negative; thymol turbidity, 1.5 units; acid phosphatase, 3 King Armstrong units; serum calcium, 10 mg per cent; serum phosphorus, 3 mg per cent; uric acid, 5.7 mg. per cent.

X-ray examination showed intense resorption of bone from the cervical, dorsal and lumbar parts of the spine. There was a collapse of the ninth dorsal vertebra, wedging of the bodies of the fifth and sixth dorsal vertebrae and of the first lumbar vertebra (Figs. 1a and 1b). There was a compression fracture of the third lumbar vertebra (Figs. 2a and 2b). Examination of the humeri (Fig. 1c) and forearms showed a moderate resorption of bone. There was marked resorption of bone in the skeleton of both hands (Fig. 3a) and moderate resorption of bone in the lower extremities, especially in the heads of the femora (Fig. 2b). There were no deformities of the heads of the femur and the lower parts of the femora were not "Erlenmeyer shaped" (Fig. 3b). The lamina dura of the teeth was intact. The intra-venous pyelogram showed normal secretion of the dye. The shape of the excretory architecture was normal.

The bone marrow puncture revealed a hypercellular marrow with an adequate number of megacaryocytes. The marrow was densely infiltrated with Gaucher cells of variable



FIG. 1a and 1b. Anterior-posterior and lateral views of thoracic spine. Generalized resorption of bone. Marked compression and wedging of D9, compression of D5 and D6. Intact pedicles and intervertebral disks.

FIG. 1c. Humerus. Bone resorption in head and superior metaphysis.

sizes. In the area where the bone marrow was intact, the distribution of cells was normal, except for a slight erythroid hyperplasia. The distribution of the different bone marrow elements was as follows: myeloblasts, 1 per cent; promyeloblasts, 4 per cent; myelocytes, 11 per cent; metamyelocytes, 4.5 per cent; polynuclear leukocytes, 21 per cent; staff cells, 9 per cent; eosinophiles, 1 per cent; lymphocytes, 1 per cent; plasma cells, 1.5 per cent; erythroblasts, 4 per cent; normoblasts, 40 per cent.

In this patient neither splenomegaly, hepatomegaly nor pingueculae were present. Her outstanding complaints consisted of back pains. The pains were due to widespread resorption of bone from the spine with compression of several vertebrae, as was readily discovered at the x-ray examination (Figs. 1a, 1b, 2a, 2b). All the intervertebral disks were intact.

A diagnosis of postmenopausal osteoporosis had previously been made and it cannot be denied that the roentgenograms of the spine are compatible with this diagnosis. Nevertheless, postmenopausal osteoporosis could immediately be ruled out because marked resorption of bone could be seen in the upper parts of the humeri which were visible on the roentgenograms of the dorsal part of the vertebral column.

In this connection it must be emphasized that postmenopausal osteoporosis is characterized by the limitation of the resorption of bone to spine, pelvis and ribs. In this disease the skeleton of the extremities and of the skull is always unaffected, at least on the roentgenograms. In contrast, in our patient radiologic examination of the rest of the skeleton revealed extensive bone resorption, both in the humeri and especially in the skeleton of the hands (Fig. 3a). There was



FIG. 2a. Anterior-posterior view of lumbar spine, pelvis and heads and necks of both femora. Generalized resorption of bone in lumbar spine. Compression of L1, compression fracture of L3. Moderate resorption of bone in pelvis and femur heads.

FIG. 2b. Lateral view of lumbar spine. Moderate compression of L1, compression fracture of L3. Intervertebral disks and pedicles intact.

also a certain degree of resorption of bone in the lower extremities; the lower parts of the femurs were not "Erlenmeyer shaped" (Fig. 3b), the heads of the femurs not abnormal (Fig. 2a). The presence of bone resorption of the hand skeleton was especially significant because this patient, a very industrious woman, used her hands regularly—if anything more than other individuals—and bone resorption by inactivity was therefore ruled out. In the absence of any clearcut cause for the bone resorption, a bone marrow puncture was deemed necessary. In the bone marrow smear large amounts of Gaucher cells were found!



FIG. 3a. Marked resorption of bone in hands. Paper thin cortex of all phalanges and of metacarpals 1, 4, and 5.

FIG. 3b. Lower half of femur. Some resorption of bone in the epiphyseal part of the femur without Erlenmeyer flask-like swelling.

Only a few cases of Gaucher's disease without hepatomegaly, splenomegaly or typical roentgen lesions of the skeleton have been reported. In this connection, the observation of Block and Jacobson (6) must be mentioned. These authors examined a woman who, in 1936 when 49 years of age, suffered from a mild normochromic anemia. In 1942 the same condition persisted. No enlargement of spleen or liver was present, x-ray examination of long bones, pelvis, vertebrae and skull revealed "normal findings". Bysternal marrow puncture, the presence of Gaucher cells was elicited. In 1948 the condition of this patient had remained unchanged. The authors mention three other reports in which cases of Gaucher's disease without hepatomegaly, splenomegaly or x-ray changes of the bones were described.

In our patient marked resorption of the bone substance of the spine and extremities with compression of vertebrae was the outstanding sign. No liver or

spleen could be palpated, and skeletal lesions, "characteristic" of Gaucher's disease, could not be found.

It is perhaps somewhat unfortunate that the so-called typical features of the roentgenological lesions of the skeleton in Gaucher's disease have been so much stressed. Cases of this disease with outstanding bone lesions occur without a so-called Erlenmeyer flask-like swelling of the lower part of the femur, without deformation of head of the femur or the humerus and without signs of bone infarction. When no "characteristic" bone lesions but only generalized resorption of bone is found in Gaucher's disease, the collective name of "osteoporosis" is commonly used as a diagnostic tag. In older women the disease then is labeled under the name of "postmenopausal osteoporosis". This is clearly illustrated by the observation of our patient.

As soon as the solidity of the spine suffers, four different roentgenologic signs develop (7):

1. In the initial stages of deossification of the spine, parts of the intervertebral disk may intrude into the softened bone of the vertebral bodies through areas of decreased resistance in the terminal plate. Usually, after some time, a sclerotic rim forms around the herniated part of the intervertebral disk. These herniations of the intervertebral disk are known as Schmorl's nodules.

2. When more intense resorption of vertebral bone substance has taken place, the horizontal trabecules of the vertebrae disappear before the vertical trabecular columns are attacked. Thus, the appearance of a vertical striation of the skeleton of the vertebrae is an early sign of bone resorption in the vertebral bodies.

3. In the later stages, wedging of the dorsal vertebral bodies develops, i.e. the anterior part of the dorsal vertebrae is more compressed than the posterior part. The diameter of the intervertebral disks of the dorsal spine does not change even if the vertebrae collapse.

4. In the lumbar spine the elastic vertebral disks impinge upon both the weakened superior and inferior aspects of the vertebrae. Thus the horizontal diameter of the intervertebral disks increases while the vertical diameter of the vertebral body itself becomes narrower and smaller. This impingement is most marked in the central part of the vertebral body and leads to the formation of fish vertebrae or hourglass vertebrae. Evidently the centrally situated nucleus pulposus has more expansile strength than the rest of the disk.

Thus, in any disease where deossification of the vertebral spine takes place, Schmorl's nodules, vertical striation, wedging of the thoracic vertebrae, and formation of hourglass vertebrae in the lumbar spine may occur. None of these phenomena are specific for any bone disease.

Although in this part of the world postmenopausal osteoporosis is the most frequent cause of widespread resorption of bone in the spine, other diseases may cause exactly the same roentgenologic anomalies of the vertebral column. However, in postmenopausal osteoporosis the resorption of bone is limited to spine, ribs and pelvis, whereas in other diseases other parts of the skeleton are also involved. It follows that the diagnosis of postmenopausal osteoporosis can never be made on roentgenograms of spine, pelvis and ribs alone. The rest of the

skeleton must also be examined roentgenographically and a diagnosis of postmenopausal osteoporosis is only permissible if the rest of the skeleton is normal. In addition, serum calcium, phosphorus, alkaline phosphatase, albumin and globulin must be determined. These values are normal in postmenopausal osteoporosis, abnormal in most other diseases which give rise to roentgenographic evidence of bone resorption in the spine. If the slightest doubt about the diagnosis persists, a bone marrow puncture must be performed.

The following bone diseases must always be considered in the differential diagnosis of postmenopausal osteoporosis (7):

a. Cushing's syndrome and longstanding treatment with corticosteroids. Deossification of the skull is present in addition to the bone resorption in the spine.

b. Osteoporosis due to senility, immobilization and avitaminosis C. The skeleton of the extremities also reveals signs of bone resorption. In avitaminosis C often subperiosteal hematomas and changes in the epiphyses are present.

c. Osteomalacia. This condition, too, involves the rest of the skeleton. In addition, calcium and phosphorus of the serum are low, the alkaline phosphatase is high. Multiple symmetrical fissures of the cortex of the diaphysis of the peripheral bones may be present.

d. In Recklinghausen's bone disease, the rest of the skeleton, especially the skull, is always involved. Cysts and osteoclastomas are often present together with subperiosteal resorption of bone in the form of disappearance of the lamina dura of the teeth, resorption of the subperiosteal bone of the medial phalanges of the fingers and of other areas of the skeleton. Hypercalcemia, hypophosphatemia, increase of the alkaline phosphatase and hypercalciuria are nearly always present.

e. Osteitis fibrosa due to chronic uremia with longstanding acidosis. This syndrome—rare in adults anyway—may cause bone changes which in many respects are similar to the anomalies found in hyperparathyroidism. However, the giant cell tumors which occur in hyperparathyroidism have never been encountered in patients with chronic uremic osteitis fibrosa. Hypocalcemia, hyperphosphatemia, hypocalciuria, increased blood urea nitrogen, low CO_2 -combining power of the serum will always be found.

f. Chronic hypoparathyroidism. In most cases the skeleton is normal but occasionally in patients with this disease widespread resorption of bone may be found. In such cases the roentgenograms of the spine may be highly reminiscent of the anomalies found in postmenopausal osteoporosis. The hypocalcemia and hyperphosphatemia which characterized hypoparathyroidism will immediately lead to a correct diagnosis.

g. Hypervitaminosis D. The generalized resorption of bone may be mainly limited to the spine, similar to the condition found in postmenopausal osteoporosis. However, usually the rest of the skeleton is also involved and metastatic calcification is a frequent occurrence. Hypercalcemia, hypercalciuria without hypophosphatemia and without an increase of the alkaline phosphatase of the serum will permit the differentiation of the two diseases.

h. Congenital hemolytic anemias, especially congenital spherocytosis. The changes of the blood picture and the decreased resistance of the red cells will permit the differential diagnosis.

i. Multiple myeloma. This disease is the most frequent source of error. In many cases it is completely impossible to distinguish between the x-rays of the spine in these two diseases, but in multiple myeloma usually the rest of the skeleton is also involved. Bence Jones proteinuria and hyperglobulinemia, if present, will easily lead to the correct diagnosis. The results of the bone marrow puncture are usually decisive.

j. Metastatic disease of the vertebral column. Search for a primary tumor will usually lead to the correct diagnosis.

As follows from the observation of our patient, Gaucher's disease must be added to this list.

The error of diagnosing postmenopausal osteoporosis on an x-ray of the spine alone without taking the precaution of studying the rest of the skeleton is frequently made. In such cases, occasionally the sudden occurrence of a pathologic fracture, involving one of the extremities, proves beyond doubt that the diagnosis of postmenopausal osteoporosis had been incorrect. In the case of Gaucher's disease reported here, the confusion with postmenopausal osteoporosis could have been avoided if the rule that the latter diagnosis should never be made upon study of the x-ray of the spine *alone* would have been adhered to. Radiologic examination of the rest of the skeleton immediately revealed that in this patient the resorption of bone was much more extensive than is the case in postmenopausal osteoporosis. It has been brought out recently that the acid phosphatase of the serum may be increased in Gaucher's disease (8). In this case, however, it was still within normal limits.

Groen (9) has stressed an interesting point to explain why Gaucher's disease is usually seen in the siblings of one generation only. He examined parents of a patient with Gaucher's disease; although the older generation did not have apparent signs of this disease, careful examination of the bone marrow of the parents often revealed the presence of a few Gaucher cells. In other words, one or even both parents of a Gaucher patient may have an incomplete form of Gaucher's disease. Several of the children of such parents may then present the complete form of the disease. The reason why the offspring of these patients with true Gaucher's disease—the second generation—usually does not suffer from this malady is not clear. Groen is of the opinion that miscarriages, stillbirths and early deaths occur very frequently in families of Gaucher patients. In addition, many patients with Gaucher's disease do not marry. These concepts, interesting as they are, have not been generally accepted.

We were therefore interested in the adult son who is the only offspring of our patient. He proved to be a normally built man, whose liver and spleen were apparently normal in size. His skeleton was roentgenographically normal and one sternal marrow puncture did not reveal the presence of Gaucher cells. The patient's parents were not available for study.

SUMMARY

A patient with Gaucher's disease is reported without palpable spleen or liver, without pingueculae, anemia, leukopenia, thrombopenia, hemorrhagic tendency or increase of the acid phosphatase of the serum.

The presenting sign in this patient consisted of severe back pains, often culminating in paroxysms of excruciating girdle pains. The pains were caused by marked resorption of bone in the vertebral column which had led to compression of several vertebrae. None of the so-called characteristic bone lesions of Gaucher's disease—Erlenmeyer-shaped lower ends of the femora, deformation of heads of femora and humeri, bone infarction—were present. The diagnosis of postmenopausal osteoporosis, which had been made previously, was proved to be erroneous when new x-rays revealed that the resorption of bone also affected the rest of the skeleton. The diagnosis of Gaucher's disease could only be made by a bone marrow puncture.

The dangers inherent in the diagnosis of postmenopausal osteoporosis, based on x-rays of the spine alone, is emphasized. A differential diagnosis of different diseases with marked resorption of bone of the vertebral column is presented.

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CHEMICAL ASPECTS OF DEFICIENCY DISEASES

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Deficiency diseases are chronic pathological conditions brought about by the continued absence of nutritional factors from the diet. For the most part, these factors are known as vitamins.

When were such diseases first observed? The annals of clinical medicine list scurvy and rickets, pellagra and beri-beri as the oldest disease entities in this group. What populations fall victim to them and where are they observed as endemic conditions? Autochthonous i.e. savage populations in most climates are able to select their food instinctively to meet their nutritional requirements just like animals do. If and where they did not, they fell prey to their deficiencies and died out.

As discovered by excavations on Denmark, a mesolithic population in pre-historic times had developed certain nutritional deficiencies as long as they subsisted exclusively on shell food. A more recent geological stratum shows that they subsequently turned to cannibalism which is in general, however, not a good regimen for collective and particularly for individual survival.

Deficiency diseases will be only endemic in relatively primitive populations under the impact of sudden unbalanced acculturation. One might consider deficiency diseases in most instances as a sequel of the white or yellow man's interference with indigenous life, in other words as a disease of colonialism. There are various mechanisms which prepare a fertile ground for deficiency disease.

(a) The increase and the improvement of general medical care which eliminates epidemics, mitigates acute disease, reduces infant mortality, and thus lowers the death rate and leads to overpopulation.

(b) The improvement of social conditions which does away with infanticide and contributes in the absence of birth control to overpopulation.

(c) The agricultural proletariat in South-Eastern Asia, especially in the Dutch East Indies, and even more so the prison population, were restricted by overpopulation and poverty to a rice diet. In this case a new factor came into play: the processing industries, which produce a more palatable or at least visually more pleasing product, in the case in point, polished rice, thus removing the hull rich in vitamin B₁. The result was thiamine deficiency: beri-beri.

(d) A factor which has not been discussed as much, namely, the tendency of the diet to become evermore monotonous. This pertains less to the meat and fish diet, which is out of reach for wide strata of the world's population, but primarily to the plant diet. As soon as agriculture produces cash crops, and turns into a business, the farmer will concentrate on the most profitable crops. In the Middle Ages millet and buckwheat were important breadstuffs, but in the 19th Century they had been almost completely replaced by the culture of wheat and

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rye with their higher yields (1). Subsequently, since 1850 the industrial revolution created a demand for the importation of wheat from overseas. Of 4000 to 5000 varieties of wheat, existing in Russian and U. S. government collections, only about four varieties are at present being planted in North America, to great acreage, because of their favorable yield and hardiness. While one would not contend in this specific instance that they are deficient in any of the vitamins, there are similar cases that may work out less favorably, whenever concrete economics get the upper hand over a vaguely known or unknown nutritional situation.

Several hundred years ago, any herbaceous vegetable was called spinach and any vegetable consumed in the form of sprouts was called asparagus. During the centuries the majority of species under cultivation fell by the wayside, turned into weeds, and eventually became obsolete or forgotten (2). What is left, is our present asparagus and our present spinach. This spinach is known to contain oxalic acid in amounts equivalent with the calcium content; the insolubility of calcium oxalate prevents the absorption of calcium in the intestine. The Chinese diet lacks, to begin with, dairy products which form the richest source of calcium in Western diets, thus it becomes calcium deficient every spring, when spinach forms the main vegetable ingredient. This is the basic cause for the endemic osteomalacia in China (3). A similar condition was discovered during the war in England, when the calcium content of wheat flour was found to be inoperative i.e. nonabsorbable because of the concomitant presence of phytic acid, which forms an insoluble calcium salt.

Adequate calcium metabolism depends on the proper absorption of soluble calcium salts in the intestine. This process requires as catalyst either exogenous calciferol (vitamin D) in countries with little sunshine or the formation of vitamin D by solar irradiation of the human body. The Chinese diet contains insignificant amounts of preformed calciferol, as it was developed by and for a people working in the fields under the plentiful sunshine of China. As soon as people with this diet congregate in cities where they are insufficiently exposed to sunshine, they develop rickets, seen in the Chinese at much earlier age than elsewhere, including fetal rickets, and osteomalacia in the adult.

The effect of citrus fruit on scurvy was known to the British in the 18th century. Since the West Indian colonies mostly produced limes, they apportioned lime juice to the sailors of the British Navy. As we now know, limes unfortunately contain substantially smaller amounts of ascorbic acid than lemons or oranges; hence, scurvy persisted on the long ocean voyages of those days and the fundamentally correct idea of prevention was temporarily discredited.

When the Spaniards undertook an expedition in 1768 up the West coast of Mexico into California to assert their sovereignty, they suffered terribly both from scurvy and from intestinal upsets. When their medical men discovered in the fall certain herbs that resembled those which they knew to be effective for intestinal trouble, the symptoms of scurvy miraculously disappeared in the patients with diarrhea, while they persisted in cases of uncomplicated scurvy (4).

While on the subject of ascorbic acid, if we ask ourselves about the supply of

this vitamin in countries outside the citrus belt, which means in Europe the part of the continent not adjacent to the Mediterranean Sea, we find that the further we go north and east across the continent, the higher the consumption of fermented foods, primarily, sauerkraut and borscht, which are a good source of vitamin C (1). On the other hand, the progressive simplification and monotony of the diet on the plantations of the Southern States of U. S., and also in poverty-ridden parts of upper Italy, with unbalanced prevalence of maize, brought, in conjunction with overpopulation and poverty, the nicotinamide deficiency pellagra.

The diet of civilized nations, on the other hand, is rarely deficient of vitamins per se. Two groups only will cause clinical problems: (a) Fadists, vegetarians, alcoholics, and other individuals with an abnormal diet, and (b) patients in whom a primary organic illness interferes with the adequate absorption or utilization of their diet.

The criteria for a complete diet are easily defined. However, subclinical and clinical deficiency, while promoting or causing malfunction or organic disease of specific tissues or organs, will not necessarily affect the total organism or impair all its functions. It was e.g. observed in the Korean war that the well-nourished G.I.'s could not carry 100 pound loads up the steep slopes and narrow trails. The calorically undernourished and partly vitamin-deficient natives found these loads no trouble at all. This should warn against onesided evaluation of the vitamin picture.

Metabolic diseases are frequently encountered in which the body requires a higher than normal quantity of certain vitamins. We may call them "relative deficiency diseases" and quote as one of the comparatively simplest examples Darrier's disease, a hyperkeratosis in which the normal daily dose of 5000-10000 units vitamin A is insufficient to prevent hyperplasia of the integument and where a larger intake and an elevated blood level of vitamin A are required to bring the skin back to its normal state (5).

In pernicious anemia the so-called intrinsic factor, which originates in the gastric mucosa is lacking. This factor is essential for the absorption of vitamin B₁₂ and its absence produces a functional vitamin B₁₂ deficiency.

At this point, another vitamin comes into play, namely, folic acid which may originate either in the food or in the intestinal flora. Folic acid assumes a formyl group (CHO) to form its active derivative folinic acid by a mechanism which somehow involves ascorbic acid; this reaction also requires vitamin B₁₂ as catalyst. For the synthesis of desoxyribonucleic acid the body needs, as key nucleotide, thymine-desoxyribotide. This is synthesized as follows: uracil, a pyrimidine derivative, is methylated to thymine with folinic acid acting as donor of the extra carbon atom. Thymine, in turn is converted into thymidine, its desoxyriboside, a reaction, in which the B₁₂-complex again acts as catalyst. The phosphorylation of thymidine, a nucleoside, finally leads to thymine desoxyribotide (thymidylic acid), the desired nucleotide, which is essential for the synthesis of the nucleic acids of the red blood corpuscles (Fig. 1). One may doubt that the enzymatic functions on vitamin B₁₂ are exhausted by those given above.

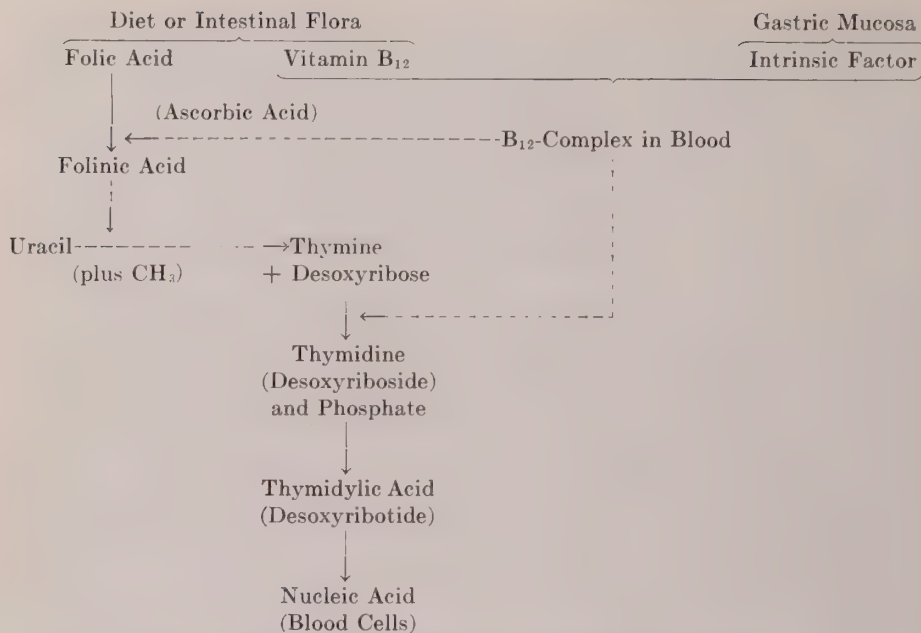


FIG. 1. Function of vitamin B₁₂ and folic acid in nucleic acid synthesis.

We have developed techniques for the microbiological assay of B₁₂ in the various fluids of the body, using *Lactobacillus leichmannii* and, in particular, the flagellate protozoa *Euglena gracilis* and *Ochromonas malhamensis*. All of these organisms are sensitive to the incredibly minute level of 1 $\mu\mu\text{g}$ per ml., which corresponds to a dilution of one part in a trillion, that is one million millions. They prove admirably suited to the assay of B₁₂ in blood serum, urine and cerebrospinal fluid (6).

Appropriate media, scrupulously free of extrinsic B₁₂, are set up with systematically rising amounts of the fluid to be tested. After an incubation period, during which the protozoa are constantly illuminated, the optical density of the cultures is determined and the B₁₂-titre is evaluated by comparison with the response to a control set, containing known amounts of B₁₂. The optical densities of such standard curves are given for all three organisms as the ordinates in figure 2; the abscissa gives the concentration of B₁₂ on a logarithmic scale. We have also developed microbiological assays for the determination of pantothenic acid and vitamin B₆ complex.

We have recently described an almost equally sensitive microbiological assay for folic acid, its conjugates, and its physiologically active derivatives. This test is based on the growth of a thermophilic strain of *Bacillus coagulans* with a temperature optimum of 55°C. As may be imagined, the use of thermophilic organisms for microbiological assays is greatly facilitated by the elevated temperature which eliminates the need for rigidly sterile techniques.

In the special instance of this bacillus we have the extra advantage that it responds not only to folic acid, but also to folinic acid and the various con-

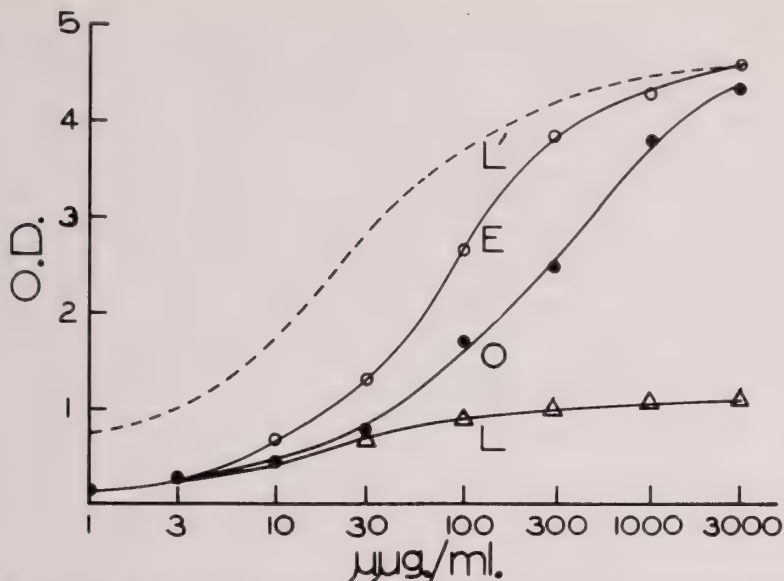


FIG. 2. Growth of *Lactobacillus leichmannii* (L), *Ochromonas malhamensis* (O), *Euglena gracilis* (E) with increasing amounts of vitamin B₁₂. The ordinate gives optical density of the cultures. The dotted line (L') gives the curve for *Lactobacillus leichmannii* with the ordinates adjusted to the level of *Euglena*.

jugates in molecular proportions. This eliminates the need for the addition of any conjugase and thus avoids the incidental addition of extrinsic folic acid.

Armed with these powerful techniques, we have studied the behavior of B₁₂ in various diseases other than pernicious anemia. We have investigated the urinary excretion of B₁₂, following the intramuscular injection of 60 µg. of this vitamin. According to Becker and Chow, the excretion is increased and the retention diminished in diabetic retinopathy. We have been able to show in a much larger number of patients that there is no statistically valid difference between diabetic retinopathy, uncomplicated diabetes, or normal individuals.

In the case of this investigation, we found increased retention and diminished excretion of B₁₂ as a specific sign in cirrhosis of the liver and during convalescence from pneumonia. In these cases, less than 10 per cent of the test dose is recovered. The usefulness of this test in the diagnosis, prognosis, and detection of liver damage is under study (7).

We have also studied the B₁₂ and folic acid content of hundreds of cerebrospinal fluids and sera from patients with multiple sclerosis and other neurological disorders. The folic acid levels in the cerebrospinal fluid in a number of the cases under study were elevated above those in normal controls. High values were scattered amongst a variety of neurological conditions, but were consistently high in cases of multiple sclerosis. While the B₁₂ level in the cerebrospinal fluid showed indifferent variations, the titre of this vitamin in the serum was also elevated in multiple sclerosis (8).

We have also used a thermophilic method for the study of folic acid in serum

TABLE I

Vitamins as co-factors in enzymatic reactions and metabolic systems

Vitamin	Enzymatic Function
Thiamine	Co-carboxylase
Riboflavin	Glycolysis (Cytochrome)
Nicotinamide	Dehydrogenases
Pyridoxal	Transaminase, Amino Acid Decarboxylase, Tryptophan Metabolism
Pantothenic Acid	Co-Enzyme A, 2-Carbon Transfer, Citric Acid Cycle, Conjugation of Bile Acids
Biotin	Fatty Acid Metabolism
Folinic Acid	Nucleic Acid Metabolism
Cyanocobalamine	Nucleic Acid Metabolism; Methyl Transfer, Choline Synthesis
Thioctic Acid	Oxidative Decarboxylation, Conjugation of Thiamine.

and urine in pregnancy. In normal pregnancy, non-complicated by anemia, B₁₂ levels are low, often almost down to the levels seen in pernicious anemia, in the maternal circulation, but high in cord blood. The folic acid levels in these cases are significantly elevated in blood and urine. These findings strengthen our concept that it is the function of folic acid to safeguard the hormonal balance and to insure normal fetal development. Vitamin B₁₂ is decreased, because it is attracted across the placental barrier by the metabolic requirement of the fetus (9).

Besides diseases brought about by dietary deficiency of one or another vitamin, there are, thus, numerous other conditions of wide variety, in which the amount of a given vitamin in the appropriate organ or tissue is inadequate, either due to malabsorption in the gastrointestinal tract or because of other abnormalities of metabolism. There are other diseases, referred to as "relative vitamin deficiencies", where supply, absorption, and transport are normal, but where pathological changes in the organ or tissue involved have raised a vitamin requirement above normal.

In other conditions, while within the normal range the vitamin content of blood and other tissues is low (or high), such findings will implicate a vitamin in the etiology of a disease and offer valuable guidance for deeper exploration. Vitamins form the coenzymes of these enzyme systems, to which the body contributes only the apoenzyme. Table I summarizes examples for these situations and indicates the enzyme systems and groups, to which the listed vitamins supply the essential prosthetic group or coenzyme. The microchemical and especially the microbiological assay of these vitamins in blood and other body fluids, often in conjunction with load tests, opens up new approaches to the knowledge of metabolic diseases.

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THE ADRENALS BEFORE ADDISON

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The completely novel and startling observation that the suprarenals are essential for life was presented by Thomas Addison¹ in 1855. Within the same year Claude Bernard² promulgated the conception of internal secretion, and in 1856 Edouard Brown-Sequard³ provided animal experimental evidence of the vital nature of the adrenals. Combined, these accomplishments raised the initial peak in the development of endocrinology. The magnitude of the sudden advance in knowledge concerning the adrenal is apparent from the fact that the role of this gland in the body was then entirely obscure. This circumstance is aptly reflected in Samuel Wilks⁴ evaluation of Addison's discovery as an achievement in anticipation of the time. Wilks wrote, "Being also in accord with Goethe, that discoveries are made by the age and not by the individual, I should consider the instances to be exceedingly rare of men who can be said to be living before their age, and to be repository of knowledge quite foreign to the thought of the time."

The validity of Wilks' appraisal is borne out by the fact that there was no significant advance in knowledge concerning the adrenal from 1855 until the discovery of epinephrine 40 years later. Nevertheless, Goethe's apothegm is still applicable, as a review of the earlier history of the adrenal will show. It is true that the original description of the adrenals by Eustachius^{5, 6} in 1563 was ignored for a long time. According to Biedl⁷, many famous anatomists of the 17th and 18th centuries failed to mention them; others, accepting their existence, endowed the adrenals with morphologic features which they did not possess and with functions which today can only be considered as bizarre or fantastic. On the other hand, the accuracy and the farsightedness of many of the early observers is impressive. The adrenal's nervous connections were recognized early in the 17th century, and in the 18th century, the relationship of abnormal foetal adrenal development to malformation of the brain was demonstrated. During the half century prior to 1855, the year acknowledged by Rolleston⁸ as "the first peak" in the history of the endocrine glands, attention was directed to the inter-relationship of the adrenals with the thymus, the thyroid, the sex glands and the lymph nodes. It had been surmised that its neurogenic medulla might place the adrenal's secretion under the influence of the nervous system. Microscopic evidence had been offered to show that the adrenal secreted a special substance into its vein. The state of knowledge concerning the adrenal at the middle of the 19th century is illustrated by the writings of Bright⁹ and Rokitsky¹⁰ which suggest that these authors might have anticipated Addison. A review of the history of the adrenals in the three centuries before 1855 will help to place Addison's contribution in proper historical perspective. This, it will be seen, will not detract from the great English clinician's individual achievement.

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ANATOMY AND PHYSIOLOGY

Bartholomaeus Eustachius Sanctoseverinatus included the first description of the adrenals, "*Glandulae Renibus incumbentes*", illustrated with drawings, in his account of the kidneys published in 1563. Piccolomini,* the next author to comment on these structures, in 1586, considered the adrenal part of the kidney which had become separated from that organ. The view that these glands served only as a support or packing for their neighboring structures prevailed for almost half a century after their discovery.

In 1611, Caspar Bartholin endowed the adrenals with the important function "of purifying or altering the black bile in some way to permit its passage through the kidneys." This was based on the erroneous description by Schenk in 1600, of a central cavity in the gland, corroborated and supplemented by Bauhin's "discovery", in 1605, of a black fluid in the cavity. Caspar Bartholin "recognized" the fluid as black bile, "*atrabilia*", in 1611, and introduced the misconception of adrenal function which was to prevail for more than two centuries. To enable the transportation of the purified black bile from the adrenal to the kidney, the elder Bartholin "suggested" a venous communication between these organs.

Thomas Bartholin,¹¹ Caspar's illustrious son, added to knowledge of adrenal anatomy† by describing accurately the arteries and the veins; Eustachius' drawings included only the veins. However, influenced by Hippocratic tradition and by his father's views, the younger Bartholin mis-named the adrenals "*capsulae atrabiliariae*" and stated erroneously that blood leaving the adrenals was conducted by a renal vein to the kidney. Many other authors, including Malphigi (1687) approved the Bartholinian misconception. Since this view could easily have been shown to depend on a non-existent venous drainage of adrenal to kidney, its acceptance over a period of two centuries can hardly be blamed entirely on the Bartholins. The fault should rather be placed on the humoral conception of medicine and the conviction it carried in an era in which inductive reasoning prevailed. This conception was so "attractive" that even after Addison had discovered the vital role of the glands, and in fact as late as 1930, a detoxifying function was still attributed to the adrenal.‡

There were several other unfounded early notions of adrenal function which were accepted for many years. Riolan, who had previously noted the gland's nervous connections and recognized the relatively large size of the adrenals in the foetus, was the first to assume (in 1629) that they functioned only in foetal life. Others shared this view or extended the period of adrenal activity to early childhood. Less plausible views were also expressed. Wharton in 1656, and later

* The monographs of Biedl⁷ and Rolleston⁸ were drawn upon for some early source material not accessible to the present author; the reader is directed to these authors for the bibliographic data not included, in such instances, in this paper.

† An excellent example of Thomas Bartholin's anatomical skill and advanced knowledge of adrenal anatomy is available in a case report of Bartholin's recently reproduced and translated by Saul Jarcho.¹²

‡ cf. S. Z. Sorkin,¹³ E. C. Kendall¹⁴.

Francis Glisson held that the adrenals received something from the spleen by the nerves common to both, which was first deposited in the central cavity and later restored to the veins. In 1675, Antonius Mollinetti assumed that the adrenals served as a "*diverticulum sanguinis foetalis*" in order to prevent blood from reaching the kidney. Even though the purpose of such a diversion of the blood was not explained, Broussais,¹⁵ as late as 1817, expressed the same belief. P. Molinetti and Pozzi (1732) believed that urine accumulated in the adrenals of the foetus. Theophile de Bordeu¹⁶ in 1752 thought that the adrenals could take the place of the kidneys in the foetus. De Bordeu, who is generally credited with the first conception of internal secretion, also endowed the adrenals with the function in foetal and adult life of separating humour from the blood, but apparently this merely implied the elimination of waste products. The proximity of the adrenals to the kidneys and the spurious central cavity offered the semblance of an anatomical basis for a possible role in urination. Although there was even less reason for connecting the adrenals with intestinal function, Senac, in 1764, stated that they produced the meconium.

Walter Charleton,¹⁷ in 1659, clearly attempted to separate the glands having no obvious ducts from those with ducts. In "*The Natural History of Nutrition*," Charleton divided the glands into three categories. The second category was characterized as "inservient to the secretion of a humor, and the reduction of it into the veins afterward". The glandulae renales or deputy kidneys were placed in this second group whose function it was to "import a humor into the veins". However, the adrenals were the only true ductless glands in the group, which included salivary and lymph glands. Furthermore, Charleton, although he envisaged the possibility of secretion into the veins by glands, cannot be credited with having harbored more than a rudiment of the concept of internal secretion.

The absence of an excretory duct was probably the source of much difficulty for the early authors. One can only be impressed with their attempts to overcome this difficulty by postulating drainage through venous channels. It is noteworthy that there was no mention of a duct until 1645, when "finally, a fallacious excretory duct was described by Severinus and then by Rhodius in 1661".⁷ According to the latter, the duct led from the adrenal to the testicle. Welsch (1691) and Droysen (1694) suggested that the adrenals were possibly connected with the thoracic duct by a special excretory duct. At about the same time, Malpighi stated that the adrenal secretion was collected by the numerous branches of a wide excretory duct and emptied into the renal vein. Kerkreng (1717) assumed that the bile-containing central cavity emptied its contents into the vena cava by means of an excretory duct. In 1719, Valsalva rediscovered a duct leading from the adrenal to the testicle. It is doubtful that he was unaware of a prior discovery of the duct by Rhodius, but Valsalva not only claimed originality for its discovery, but, Rolleston⁸ tells us, "entered a public protest" in Italian literary journals lest someone else claim credit. Ranby, in 1725, and Duvernoy later suggested that Valsalva's "duct" was probably the spermatic branch of the

renal artery. The fact that the existence of one excretory duct was not possible of proof did not prevent Beudt (1744) from describing two ducts leading to the pelvis.

The first author to state clearly that the adrenal gland had no excretory duct and that this was one of its essential characteristics, was a French physician whose identity has remained undisclosed. The Academy of Sciences at Bordeaux in 1716 chose as the subject for a prize competition: "The Function of the Renal Glands or Atrabiliary Capsules". Montesquieu, whose place in medical history has been stressed recently by Camille Dreyfus,¹⁸ was appointed judge. In an address before the Academy in which he, incidentally, displayed a comprehensive knowledge of the adrenal gland, Montesquieu said: "Another who fortunately defined the difference between conglobated and conglomerated glands considered the atrabiliary capsules a conglobated one. He believes that they are a continuity of vessels in which the blood like in channels is subtilized. . . . In these glands, and in every conglobated gland, there is no excretory duct, because there is no matter to separate liquids, but only to subtilize them." Montesquieu found "this system not without some appearance of truth which is captivating at first," and stated that it attracted the attention of the Academy. However, since the contestant was unable to defend his thesis to the satisfaction of the Society, the prize was not awarded and his identity remained undisclosed. As a further misfortune, these facts did not become generally known until Caillaud called attention to Montesquieu's address¹⁹ in 1819.

During the 18th century there was advance in knowledge of adrenal anatomy, the ductless nature of these organs received further recognition and there was significant progress in the development of the concept that the ductless glands poured a secretion directly into the blood stream.

Morgagni²⁰ noted, in 1719, that the suprarenal and the kidney had a common fascia, and in 1733 was the first to describe the occurrence of accessory adrenals in man. These structures, described in greater detail by Duvernoy in 1741, were apparently first noted in dogs by P. I. Hartmann in 1699.

Authentic information concerning adrenal anatomy became generally available following the publication of Jacques Benigne Winslow's²¹ classical description of the human adrenal gland, in 1732, and the appearance of the new editions of Eustachius' anatomical charts by Albinus in 1761 and Lancisius in 1769. English translations of Albrecht Haller's²² lectures appearing about this time stated, "the adrenal has no visible excretory duct, nor does it discharge any juice, by visible pores into the vein."

In 1761, Haller²³ grouped together thyroid, thymus and spleen "as ductless glands which pour a special substance into the veins and so into the circulation." This was a radical departure from the views of Galen, prevailing since the 2nd century A.D., that the pituitary discharged pituita (phlegm) into the nasal cavities and that the secretion of the thyroid lubricated the larynx. Rolleston⁸ states that this view of pituitary function was disproved by Conrad Victor Schneider in 1655 and by Richard Lower who suggested in 1670 that its secretion

"distills not upon the palate but is poured again into the blood and mixed with it". However, this suggestion appears to have received little attention at the time. Galen's primitive notion of thyroid function was replaced in the mid-18th century. According to Albrecht Haller, F. Ruysch and other writers were then of the opinion "that a peculiar fluid was elaborated in the thyroid and poured into the veins".

In 1775 Theophile de Bordeu* maintained that each organ of the body gives off "emanations which are necessary and useful to the whole body". He stated that "each (of the organs) serves also as a factory and laboratory for a specific humor, which it returns to the blood after having prepared it within itself and imparted to it its own intrinsic character". His writings stressed the idea that the secretions were poured into the blood stream and he believed that this could be demonstrated by examining venous blood. "This assertion as to continual emanations from each organ into the blood I regard as medically proven." His views were convincing, especially his deductions concerning the tonic effects of gonadal secretions and their long-known influence on the secondary sex characteristics. However, they were without experimental foundation and thus had no definite influence on contemporary medical thought.†

At the beginning of the 19th century, Johann Friedrich Meckel,²⁶ who had at his disposal the zoological collection of the Jardin des Plantes, ascertained the important fact that the suprarenals were present in all mammals, and made other important observations from his studies in comparative anatomy. This field had been a source of knowledge concerning the adrenals since the mid-17th century and, between 1816 and 1846, other authors supplemented Meckel's work by demonstrating the presence of adrenals in fishes and reptiles.

It is interesting to note that Meckel sought to establish a relationship of the adrenals to the thyroid and the thymus. The large thymus of the calf and sheep foetus compensated, in his opinion, for the small adrenals. He believed there was a closer relationship between the adrenal and the thymus because the thymus disappears entirely in animals which have large adrenal and thyroid glands. In contrast to the relationship which he found in these widely separated organs, Meckel perspicaciously stated that the relationship of the adrenals to the kidneys consisted only in their being neighbors.

In the human adrenal Meckel differentiated the more solid yellow substance, cortex, from the inner, softer, reddish-brown medulla. The final refutation of the presence of a central cavity was presented by Nagel,²⁷ in 1836, who showed by means of injected preparations that the large central vein had been mistaken for a central cavity.

Microscopic evidence of a secretion by the adrenal into its vein was offered by

* cf. H. D. Rolleston⁸, H. Grasset²⁴, M. Neuburger²⁵.

† Nevertheless, Grasset²⁴ and, especially, Max Neuburger²⁵ credit de Bordeu with the first formal suggestion of the modern concept of internal secretion. Neuburger considered de Bordeu to have been the sole "precursor to Brown-Sequard, the founder of the doctrine of internal secretion".

George Gulliver²⁹ in 1840. Four years earlier T. Wilkinson King²⁸ of Guy's Hospital, described the colloid of the thyroid gland and showed that it passed into the lymphatics and so into the great veins. He suggested, "we may be able to show that a particular material is slowly formed and partially kept in reserve, and that this principle is also supplementary, when poured into the descending cava, to important functions in the course of circulation." Gulliver described spheroidal bodies in the adrenals and in their veins, "probably the excretory ducts of the gland", and stated that the adrenals "poured into the blood a peculiar matter which has doubtless a special use". This description has been considered by Rolleston as having equal merit with Vulpian's³⁰ demonstration in 1855 that the adrenals discharge into the blood a substance which they alone elaborate. He observed that the medulla of the adrenals and the blood in the adrenal veins stained an emerald-green color with iron perchloride, a reaction not obtained in other organs or in the blood elsewhere in the body.

In 1841, Henle³¹ grouped the adrenals with the "Blutgefaessdruesen", thyroid, thymus and spleen, and expressed the thought that these glands altered the composition of the blood by withdrawing from it certain substances which were further developed in the parenchyma of the gland and then returned via blood or lymph vessels. However, he doubted that the adrenals could be grouped with the other Blutgefaessdruesen as rightfully as with the neurological organs.

A highly important new chapter of adrenal research was initiated by the histological studies of Ecker,³² published in 1846, in which he described, in accurate detail, the connective tissue framework of the adrenal, the closed parenchymal tubular structure of the cortex and the nervous tissue components of the medulla. Accessory adrenals were found to be made up principally of cortical tissue and did not contain any medullary substance. From an examination of the adrenals of all four classes of vertebrates, it was concluded that the microscopic structure is essentially alike in all. He demonstrated the lack of structural development in the adrenal during foetal life despite the relatively large size of the gland during that period. Careful evaluation of histological observations led him to the deduction that the adrenals, and other blood-vessel glands, formed a secretion from the blood which was returned directly, or via the lymphatics, to the blood stream. The neurogenic composition of the medulla did not lessen his conviction that the adrenal was a true "Blutgefaessdruese",³³ but suggested the possibility that the adrenal secretion might be under the influence of the nervous system. A fundamental description of adrenal histology by Koelliker³⁴ in 1854 stressed that the cortex and medulla were functionally distinct from each other.

EMBRYOLOGY

Although there are but a few reports on the embryology of the adrenal gland prior to 1855, these express a fairly accurate conception of its development. In 1831, F. Arnold³⁵ stated that the adrenals developed from the Wolffian bodies by means of a fissure. Henry Gray,³⁶ in a paper on the development of the ductless glands in the chick, in 1852, concluded that the suprarenals arose from two masses of blastoma lying between the Wolffian bodies and the aorta. A few

years before this, Remak^{37, 38} had indicated that the adrenals were embryologically related to the sympathetic ganglia.

PATHOLOGY

The first formal presentation of adrenal pathology appeared in Matthew Baillie's³⁹ "The Morbid Anatomy of the Most Important Parts of the Human Body", published in 1793. This book, described by E. R. Long⁴⁰ as "The first text of pathology devoted to that science exclusively by systematic arrangement and design", included a few short paragraphs under the heading "Diseased Appearances of the Renal Capsule". It was Baillie's further merit, in a second edition, 1797, to provide the first description of adrenal tuberculosis. Under the heading "Adrenal Capsule Scrofulous", he wrote, "It has occurred to me to see only one instance of scrofula in the renal capsules. In this case, the renal capsule affected by it was very much enlarged in size, being nearly as large as a kidney, and was changed into the same kind of white matter, which is observable in a scrofulous absorbent gland." However, even with this addition, the section on adrenal pathology did little more than emphasize the belief which prevailed for almost three centuries after Eustachius' description of the adrenal glands, that these organs were rarely the site of significant disease.

Some interesting, though sparse and uncodified observations of adrenal pathology were recorded prior to Baillie. In 1679, Theophile Bonet,⁴¹ in his "Sepulchretum Sive Anatomia Practica",* mentioned scirrhus adrenals in a case of dyspnea with various affections of the chest and abdomen. Morgagni,⁴² in "De causis et sedibus morborum" in 1733, included the description of a glandular tumor involving the left adrenal and kidney contiguously. This was an incidental finding in a case in the section on thoracic diseases. Other early reports of neoplastic involvement of the adrenal by Soemmering⁴³ and Meckel²⁰ appeared after 1800. According to Meckel, Morgagni was the first to observe that the adrenals were decreased in size in acephalous fetuses. Other early observers of this relationship were Renard,⁴⁴ and Hewson and W. Cooper,† prior to 1755, and Soemmering who made corroborative observations a few years later. An early report of a case in which the adrenals were transformed into a cartilaginous substance is cited by Soemmering⁴⁶ in an annotated translation of Baillie's text.

Joseph Lieutaud's "Historia Anatomica Medica", edited and enlarged by Portal⁴⁷ in 1767, contains the first compilation of adrenal necropsy findings. Under the heading "De Renibus et Capsulis" and subheading "Capsulae atrabiliariae morbosae", are short abstracts of clinical and pathological findings in four cases observed by Greiseli, Blasius, Bartholinus and Portal, respectively.

* A collection of nearly 3000 necropsy protocols drawn from many sources.

† Cooper, W.—"Mr. Hewson, some time before his death, seemed to be confirmed in the opinion that whenever children are born with little or no brain, the capsulae renales are always very much diminished. This is certainly the case in one or two brainless children which I have by me and whose renal capsulae he examined, with a view of being further satisfied upon this subject."⁴⁵

These observations are of little value since their brevity makes it almost impossible to reconstruct the pathology. However, Lieutaud's treatment of the adrenal as an organ worthy of consideration in a system of special pathology may have led Baillie to do likewise.

In 1814, Otto⁴⁸ wrote in his "Handbuch der pathologischen Anatomie des Menschen und der Thiere", that the adrenal could be inflamed, suppurated and deteriorated, hardened, scirrhou and cancerous. He also stated that the substance of the glands could sometimes be entirely lacking without having been destroyed by suppuration.‡ As an interesting finding, he reported a case in which adrenals twice the normal size were found in association with overly marked development of the genitalia in a male.

The interest at Guy's Hospital in morbid anatomy and in the suprarenal bodies is reflected in Thomas Hodgkin's⁴⁹ "A Catalogue of the Preparations in the Anatomical Museum of Guy's Hospital", published in 1829. Hodgkin, then the professional pathologist to the hospital, deduced that the renal capsules and the kidneys were independent of each other with respect to their derangements.§ He wrote, "The renal capsules were found variously disorganized, whilst the kidneys are little, if at all, affected. On the other hand, the kidneys may be so completely wasted, as to be scarcely discoverable, whilst its corresponding capsule retains its ordinary size and natural appearance." In the museum he retained three normal foetal adrenals, two examples of "fungoid" (metastatic neoplastic) disease, one of which was associated with an accessory adrenal, and an example of a similar body in a foetus. He noted, "It would seem that accessory bodies of this kind though not invariably, are frequently present, and are liable to enlargement from disease."

Another of "The Great Men of Guy's", Richard Bright,⁹ might have anticipated the discovery of Addison's disease by almost twenty-five years. In 1829, Bright reported "Serous effusion under the arachnoid and into the ventricles in a case of emaciation with bilious vomiting and diseased renal capsules." He described the morbid change in the adrenals as "scrofulous suppuration", and he placed the capsules in the pathological museum. Bright's description of the clinical features included emaciation and bilious vomiting (mentioned in the title of the report), and he noted the patient's very dark complexion, but he failed to correlate the clinical manifestations with the diseased state of the adrenals.

The first report of massive hemorrhage into the adrenal was published by Rayer,⁵⁰ an illustrious member of the Parisian school which flourished at the beginning of the 19th century. The titles of two of his three case reports reveal a thorough understanding of adrenal apoplexy: "Case 1: A huge tumor in the right side, arising from an enormous apoplexy of the right adrenal"; "Case 3: Umbilical hernia in a new-born; hemorrhage in both adrenals resulting in tumors

‡ It was not possible to determine from the text whether Otto was describing advance 1 cytotoxic atrophy.

§ Rayer⁵⁰ (1837) and Boyd⁵¹ (1841) reported malformations similarly illustrating the independence of these two organs.

in the flanks." Rayer* presented a rather complete account of adrenal pathology based on a careful review of the literature and on his own observations. Questioning Meckel's belief concerning a direct adrenal sex-gland relationship, he examined and found the suprarenals to be normal in a number of cases of testicular and ovarian disease. He concluded that this approach failed to provide proof of such a relationship, but was careful to leave open the possibility that it might nonetheless exist.

Only a few years later, Rokitsansky,⁵² the great Viennese pathologist, rendered an advanced presentation of adrenal pathology in his "Handbuch der speciellen pathologischen Anatomie", published in 1842. Reference was made to a decrease in size of the adrenal resulting from disease and to occasional complete absence of the gland due to developmental anomaly. Contraction of the cortex into a leathery tough substance and obliteration of the medulla was described, as was also induration atrophy following inflammation. Tuberculous and cancerous degeneration of the adrenal were found to occur not infrequently, the former being more common. Concomitantly, similar involvement was also noted elsewhere, especially in the lymph nodes. This was probably the basis for the interesting statement in his introductory paragraph that diseases of the adrenal were more directly related to diseases of the lymph-gland system than to the kidneys or sex glands.

Rokitansky found the tubercle to be deposited in large masses in the adrenal, either in confluent form contained in a callus-walled pus-sac or as a chalky concretion enclosed in fibroid connective tissue in which *all traces of suprarenal substance* were absent. It is tempting to speculate why this latter observation did not lead its author to seek out associated stigmata and thus anticipate Addison's discovery. Even though he, personally, performed and wrote the protocols of almost 30,000 necropsies during a period of 35 years, Shryock⁵³ tells us that his description of a case was not merely anatomical. It included a consideration of the etiology and the development of the condition encountered at autopsy, as well as the functional derangement involved.

Klemperer⁵⁴ states, "In his farewell address, Rokitsansky could justly assert that he had pursued pathologic anatomy as a scientific vocation aimed at fertilizing clinical medicine." Indeed, his contributions helped to complete the establishment for many diseases of a nosological concept on a definite morbid anatomical basis rather than on symptoms. On the other hand, he also elaborated an almost entirely speculative doctrine of humoral pathology which referred all diseases, in a final analysis, to some abnormal state of the blood. These views, which he later abandoned following their denunciation by Virchow† in 1850, may have inclined Rokitsansky to be more concerned with the cause of adrenal gland destruction than with its effect, a circumstance which would tend to lead him away from the discovery which Addison was soon to make.

* He was also noted for his thorough presentation of other subjects, and as the author, according to E. R. Long,⁴⁰ of the first History of Pathology.

† cf. R. H. Shryock.⁵³

CONCLUSION

In the three centuries following its discovery by Eustachius in 1563, there accumulated a fairly large body of information concerning the anatomy and histology of the suprarenal gland. Found to be present and of comparable histological structure in all vertebrates, this organ had emerged as a ductless gland composed of a cortex and medulla. On the basis of common anatomical features it was grouped with the thyroid, thymus and spleen as the "blood vessel glands." Microscopic evidence was presented to show that the thyroid and the adrenal elaborated an internal secretion which was held to be of special use in the body. Knowledge in morbid anatomy had progressed to the point at which it was recognized that the adrenal could be involved in many disease processes, but the idea that it could be the seat of a significant primary affection had not been broached. There appears to be no record prior to 1855 of anyone having associated definite symptoms, let alone a characteristic disease picture, with morbid change in the adrenal, nor of any attempt to discern the gland's function from this change. Definite knowledge of the function of the adrenal, normal or diseased, was strikingly absent. It was Addison's achievement to provide, in his words, a "first and feeble step towards inquiry into the functions and influence of these organs". This step was, however, far from feeble. In his monograph, "On the Constitutional and Local Effects of the Suprarenal Capsules", published in 1855, he proved that the adrenal glands are essential for life.

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OBSERVATIONS ON THE PATHOGENESIS AND SEQUELAE OF INTERSTITIAL INFLAMMATION AND FIBROSIS OF THE LUNGS

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Ever since Hamman and Rich (1) described several cases of acute interstitial fibrosis of the lung, and Baldwin, Cournard and Richards (2) defined the associated physiological dysfunction as an alveolar-capillary block, most conditions with diffuse interstitial pulmonary involvement have been indiscriminantly classified as the Hamman-Rich syndrome. This was never the intent of these investigators either on clinical, anatomic or physiologic grounds. Nevertheless, increased attention is being focused on those pulmonary conditions in which the basic alteration consists of diffuse interstitial inflammation with varying degrees of fibrosis. Many questions pertaining to this group of lesions are only partially answered and others remain an enigma. Is this type of pulmonary alteration increasing in frequency? If so, what are the reasons? What are the known causes for diffuse pulmonary inflammation with fibrosis? What is the pathogenesis of these lesions? Are there other sequelae to these lesions besides the respiratory and ventilatory disturbances, such as the development of terminal bronchiolar carcinoma?

In order to evaluate some of these problems an extensive group of autopsied cases with interstitial pulmonary changes were reviewed within the context of the above questions. Auerbach and his associates (3) analysed pulmonary fibrosis as to its incidence in autopsies in the periods before the use of antibiotics and since their inception. They concluded that there is a definite increase in the incidence of pulmonary fibrosis in the recent period. They found that in 12 per cent of the recent autopsies pulmonary fibrosis was present as compared to seven per cent in the pre-antibiotic period. These investigators excluded from both series of cases fibrosis related to such conditions as tuberculosis and bronchiectasis.

The present study was not approached from a statistical point of view, but it appears that interstitial pulmonary fibrosis, unrelated to tuberculosis, bronchiectasis or suppurative pulmonary disease, is observed at post-mortem examination more frequently than in previous years. The possible reasons for this will be commented on later. Although it is only recently that considerable attention is being focused on the various aspects of pulmonary fibrosis, it is of historical interest to note that Corrigan (4) in 1838 described a pulmonary condition as cirrhosis of the lung. At first glance, one might think that he was referring to diffuse interstitial fibrosis of the lung which in some respects could be properly called "cirrhosis of the lung". Careful analysis of his own description indicates, however, that he probably was dealing with bronchiectasis complicated by episodes of organizing pneumonia. These eventually led to extensive fibrosis and contracture of the lung. In fact, Corrigan stated, "the second and third rate

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bronchial tubes as they proceed in their course, instead of growing smaller, are dilated and end in cul-de-sacs, while on the side of these cul-de-sacs are seen the orifices of the still smaller branches; these smaller branches on examination are found to be impervious".

Prior to the antibiotic era, studies on the lungs of fatal cases of influenzal pneumonia, particularly shortly after World War I, revealed that the pulmonary lesions were those of diffuse interstitial inflammation.

Diffuse forms of interstitial inflammation and/or fibrosis of the lungs may be divided into several broad groupings.

1. Those in which the agents causing the interstitial alterations are clearly known and at times demonstrable, or those in which the alterations are specifically related to a definite disease syndrome. In this category, one might include berylliosis, Boeck's sarcoid, hematogenous miliary tuberculosis, atypical forms of lipid pneumonia, toxoplasmic pneumonia and rickettsial pneumonia.

2. Those in which the interstitial changes are associated directly or indirectly, with some definite disease entities, such as scleroderma, lupus erythematosus, and perhaps rheumatoid arthritis. In these situations the damaged lungs reveal no histologic changes that are specifically related to the basic or associated systemic disease process.

3. Those in which the interstitial changes are secondary to basic disturbances in the lungs, such as chronic pulmonary congestion with or without superimposed secondary infection. Examples of this would be the alveolar wall thickening in chronic pulmonary congestion, particularly secondary to mitral stenosis. Recent evidence, however, tends to minimize the role of congestion secondary to mitral stenosis as a pathogenetic mechanism whereby alveolar wall fibrosis may develop. Another example would be the fibrosis of the lungs that has been observed with hexamethonium therapy for essential hypertension. Recently it has been postulated that the methonium salts produce pulmonary fibrosis not as a result of congestion, but because these salts are directly irritating to the lungs (5).

4. Those in which a specific acute infection can be identified such as the atypical pneumonias. These are generally regarded to be viral in origin. A specific viral pneumonia of this type would be psittacosis.

5. Finally there are the cases of indeterminate diffuse inflammation and fibrosis in which no etiologic mechanism is demonstrable. These often have an insidious onset and demonstrate varied but usually relentlessly progressive courses.

It is this latter group about which this report is mainly concerned. In order to correctly evaluate this latter group, cases that do not properly fit the criteria must be excluded. For instance it has been noted that some cases included and even reported in the literature in this group are on careful scrutiny cases of diffuse bronchiolectasis in which repeated infection has terminated in diffuse fibrosis of the lungs. In this end-stage picture the primary role of the diffuse bronchiolectasis may be ignored or misinterpreted.

These indeterminate interstitial fibroses do not necessarily follow the pattern and course described by Hamman and Rich. They delineated a rather precise clinical pathological syndrome that perhaps began with a vague upper respiratory

picture and usually terminated fatally within a matter of a few months either from the pulmonary or cardio-pulmonary insufficiency. Interstitial fibrosis of the lungs does not necessarily follow this course. Some may progress just as rapidly while in others the lesions may develop slowly over a period of a year or two, and still in others it may persist for five years or longer (6). The histologic alterations in the alveolar walls vary with the duration and intensity of the process so that in those of short duration there is a greater degree of inflammation relative to the fibrosis. Those lasting a year or so will have more fibrosis, and those extending over many years reveal alveolar walls with considerable amounts of well developed collagen and only scant evidence of inflammation. Regardless of the duration of these cases it is difficult to determine the etiology.

Perhaps one of the difficulties that has been encountered in uncovering etiology agents is the rigid application of certain concepts, such as the concept that only those ducts that contain silica are fibrogenic. Although this may be accurate in its strictest sense, it is also possible that other inhaled irritants or atmospheric pollutants may produce low grade chronic inflammatory processes with fibrosis even though the irritants in themselves may not be directly fibrogenic. The concept that some irritants only cause acute inflammation and upon subsidence leave no sequela may also be unfounded. Some irritants may not only evoke a sub-clinical interstitial inflammation that may become organized, but may also initiate an intra-alveolar inflammatory response in which the exudate contains disproportionately large amounts of fibrin relative to the number of polymorphonuclear leucocytes present. In such situations as uremic or post radiation pneumonitis there is considerable fibrinous exudate associated with scant numbers of polymorphonuclear leucocytes (Fig. 1). There is also considerable fibrin and leucocytes present in the pneumonitis associated with the administration of methonium salts. Inhalation of carbon tetrachloride reveals essentially the same findings in the lungs. Pulmonary viral infection will also tend to show fewer polymorphonuclear leucocytes than that usually seen in bacterial infections.

The intra-alveolar fibrin produced by these varied noxious agents (during periods of forced ventilation) often becomes plastered up against the alveolar wall into what has been commonly referred to as a hyalin membrane. These (fibrin) hyalin membranes are obviously not specific and are seen in a wide variety of conditions. In a recently encountered case of carbon tetrachloride poisoning postmortem examination revealed fibrin membranes lining the alveolar walls and only a slight inflammatory cell response was present. Partially organized fibrin was also present within the alveolar walls (Fig. 2). The significance of this relative to the subject under decision resides in the fact that if this patient had survived the acute poisoning, as many do, it is conceivable that a certain amount of fibrosis may have developed and remained in the lungs of this individual. In most instances it is most likely focal and would produce no clinical picture.

The significance of this disparity between the amount of fibrin in the alveolar exudate and the number of polymorphonuclear leucocytes relative to the eventual development of interstitial fibrosis of the lung has been commented on by Auer-

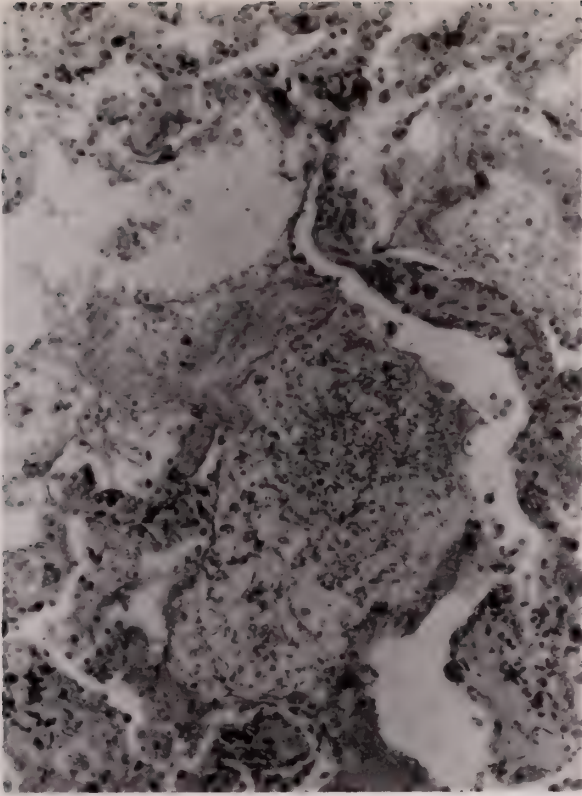


FIG. 1. Photomicrograph showing alveolus with exudate consisting predominantly of fibrin and red blood cells. Leucocytes are scant.

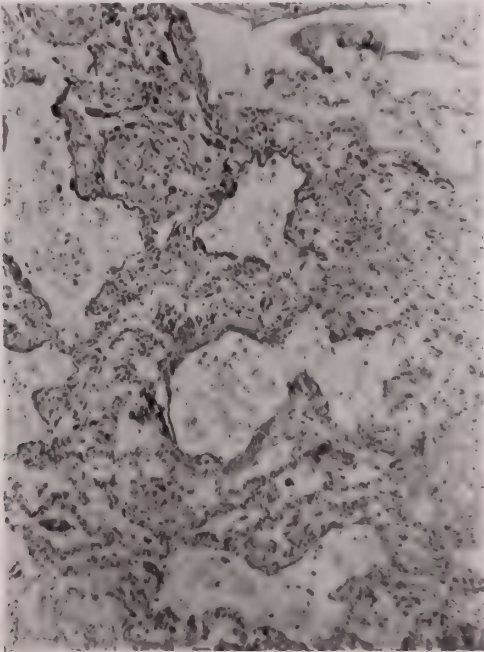


FIG. 2. Photomicrograph of a fatal case of carbon tetrachloride poisoning in which the lungs show fibrin lining the alveolar wall with beginning interstitial organization.

bach and associates (3) in reference to the increase in the incidence of fibrosis of the lungs. These investigators postulated that this phenomena may occur in antibiotic treated pneumonias and have theorized that this relative lack of polymorphonuclear leucocytes leads to inadequate fibrinolysis. It has been known for years that fibrinolysis is to a great extent dependent upon the release of enzymes from polymorphonuclear leucocytes (7). If these cells are not present in sufficient numbers intra-alveolar fibrin may not be lysed and remains as a stimulus and scaffold for fibroblastic proliferation. This fibrin may become incorporated within the wall of the alveolus or at least alongside of it, and thus thicken it. It is possible to extend this mechanism postulated by Auerbach to many types of pneumonia in which this disparity between fibrin and leucocytes exists. If it is then recognized that a variety of inhaled irritants may evoke a fibrinous response in the lungs it becomes necessary to search into the background of these individuals for any such exposure no matter how inconsequential or fleeting it may have appeared at the time of the actual event.

Relative to this same mechanism one might account for the cases reported as interstitial fibrosis of the lungs in rheumatoid arthritis. Most of these cases are treated with corticosteroids. These steroids inhibit the usual inflammatory response, may mask infections in the lung, and has been responsible for the occurrence of agranulocytic forms of pneumonia (Fig. 3). Upon discontinuation of therapy, these predominantly fibrinous pneumonias may organize. Thus, the

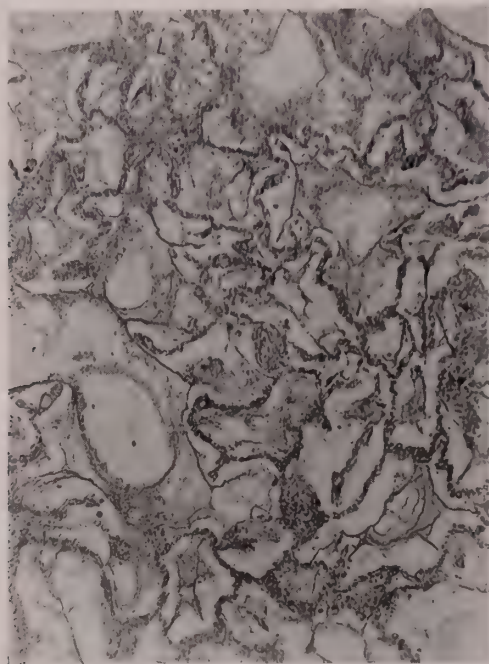


FIG. 3. Photomicrograph from a case of rheumatoid arthritis that received intensive corticosteroid therapy. This shows an agranulocytic pneumonia with considerable fibrin present.

fibrosis reported to be associated with rheumatoid arthritis may be related more closely to the form of therapy rather than to the basic underlying disease process.

In any inflammatory and fibrotic process involving the alveolar walls the elastic tissue is disrupted and fragmented. It has been demonstrated that fragments of elastic tissue may act in as a foreign body and provoke a fibrogenic and foreign body giant cell reaction within the alveolar walls (8). Thus any chronic inflammatory process with fragmented elastic tissue, even though the original irritant, is no longer present, may reveal progressive alveolar wall changes. In a number of these cases of protracted interstitial fibrosis numerous giant cells are seen in the alveolar walls, as well as bits of disrupted elastic tissue.

The increase in incidence of atypical pneumonias relative to the incidence of bacterial pneumonias may account for some increase in interstitial pulmonary fibrosis. In addition antibiotics have altered the bacterial flora of the tracheo-bronchial tree, and in this manner may possibly permit the development of sub-clinical forms of chronic low grade infection with fibrosis. In many of these cases an alveolar capillary block eventually appears. It is this functional impairment that ultimately results in the respiratory or cardio-respiratory insufficiency that imparts the serious clinical significance to this lesion. Recent evidence (9) indicates that alveolar-capillary block may not be the only serious sequella of chronic interstitial inflammation and fibrosis of the lung. Beaver and Shapiro (9) have recently reviewed all of the reported cases of alveolar cell carcinoma and they speculate that many of these arise upon a background of chronic parenchymal pulmonary inflammation and fibrosis. I have had occasion to observe a number

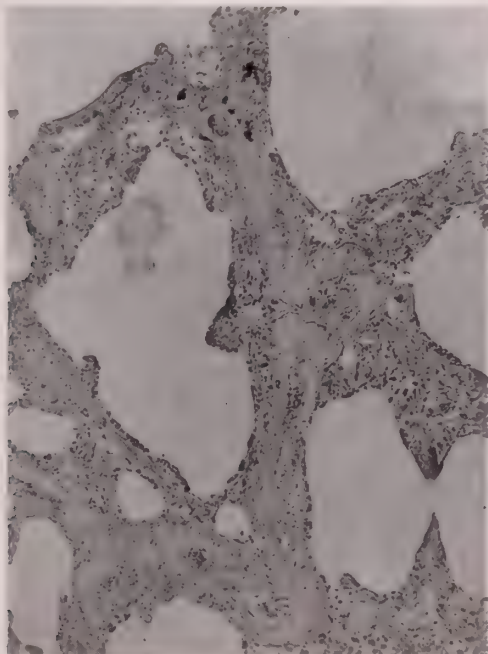


FIG. 4. Photomicrograph showing a diffuse interstitial fibrosis.

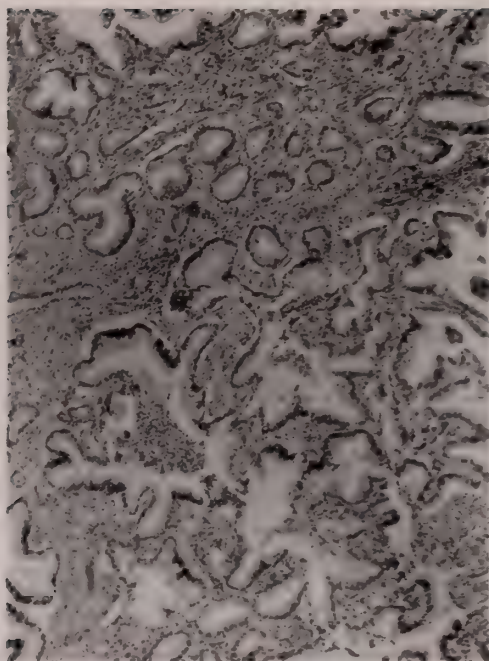


FIG. 5. Photomicrograph from the same case as figure 4 showing terminal bronchiolar carcinoma.

of cases of terminal bronchiolar carcinoma (alveolar type) in which there was a background of fibrosis of the lungs. In nine of these cases the fibrosis was diffuse and predominantly interstitial (see Figs. 4 & 5). In a tenth case there was an old tuberculous scar present at the site of origin. Carcinoma of the lung has also been noted to develop in association with fibrosis of the lungs that is seen in scleroderma, and is also seen at the periphery of healing pulmonary infarcts. All transition forms ranging from hyperplasia of the alveolar or terminal bronchiolar lining to carcinoma may be observed under these circumstances. In many of these cases considerable fibrosis is present in areas removed from the carcinoma. Since this form of carcinoma does not block any significant sized bronchus, infection with subsequent fibrosis does not develop secondary to it. An analogy might be made between this situation and that seen in cirrhosis of the liver. Fibrosis of the liver with regenerative hyperplasia of liver cells develops from a background of varied etiologies and often ends with a liver cell carcinoma. Similarly in the lungs, secondary to a variety of causes, fibrosis of the lung may develop with alveolar cell hyperplasia that may ultimately lead to terminal bronchiolar (alveolar type) carcinoma. Further investigation is obviously necessary concerning this situation.

CONCLUSIONS AND SUMMARY

1. Diffuse interstitial inflammation and fibrosis of the lung is a lesion that has increased in incidence in recent years.

2. This lesion is a response to a wide variety of noxious agents that may enter the lung.

3. Aside from such specific conditions as Boeck's sarcoid, berylliosis etc., there are no specific histologic alterations in this lesion that enable one to set one case apart from another as to etiology.

4. Such noxious agents as carbon tetrachloride, viruses and such forms of therapy as antibiotics, methonium salts and corticosteroids, may evoke or alter the inflammatory responses in the lung so that a disproportionate amount of fibrin may be present relative to the number of polymorphonuclear leucocytes, and thus interfere with fibrinolysis and set the stage for organization.

5. In addition to the functional disturbances of alveolar capillary block, an uncommon but important sequela of chronic inflammation and interstitial fibrosis of the lung may be the development of terminal bronchiolar carcinoma (alveolar cell type).

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ENDOCARDIAL SCLEROSIS IN INFANCY ASSOCIATED WITH ABNORMAL STORAGE (GARGOYLISM)

REPORT OF A CASE IN AN INFANT, AGED FIVE MONTHS AND REVIEW
OF THE LITERATURE

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Endocardial sclerosis is among the more uncommon forms of congenital heart disease, its incidence being estimated at seven per cent (1). Although the anomaly is congenital clinical manifestations may not become apparent until a few weeks or months after birth. Death may ensue rapidly after the onset of symptoms, or after a more protracted course with repeated attacks of congestive heart failure. As a rule the disease is fatal under the age of one year. Its etiopathogenesis has been the subject of various theories. Among these, fetal infection or inflammation (2, 3), anoxia (4), malformation (5, 6), hemodynamic disturbances (7), metabolic disorder (1), and even "collagen disease" (8), have been favored. When unasociated with major cardiovascular anomalies endocardial fibro-elastosis appears to constitute a distinct entity with a significant familial incidence indicating an underlying genetic mechanism (1). Recently, Kelly and Andersen (1) have suggested that the endocardial changes are the result of a familial metabolic disorder of the myocardium.

It is known that inborn errors of metabolism may involve the heart as in cardiac glycogen storage disease and in gargoylism. While death from cardiac failure in early infancy is the rule in the former condition, it is considered very rare in gargoylism (9).

The case reported in the following, of a five months old infant with clinical and gross anatomical features of congenital endocardial sclerosis, and microscopic findings typical of gargoylism, is therefore of uncommon interest.

REPORT OF CASE

E. H. (adm. #51191), a 4½ months old American negress, was admitted to the Pediatric Service of The Mount Sinai Hospital on August 7, 1955, because of respiratory difficulty starting eight hours earlier. Three weeks before, she had been treated in the emergency ward for an upper respiratory infection. She had improved except for occasional mild cough. She was the only child of apparently unrelated, healthy parents. Except for diabetes of the maternal grandmother, no history of familial disease was elicited. The patient was born by spontaneous delivery after a normal full term pregnancy. The birth weight was 3500 grams. There were no neonatal difficulties. Except for skin eruptions attributed to orange juice she presented no abnormalities, and her physical and mental development was considered in

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FIG. 1. X-ray of the chest showing marked enlargement of the transverse diameter of the heart, and some broadening of the costal diaphragses.

keeping with her age. She appeared to be a normal, healthy baby until her first episode of upper respiratory infection with otitis, three weeks prior to her first hospitalization.

Physical examination revealed a well-developed, "obese" infant, weighing 7220 grams. She was acutely ill, in respiratory distress, with rapid, shallow respirations at the rate of 50 per minute, and costal retractions, but without cyanosis. The temperature was 38°C., the ventricular rate was 200 per minute, with gallop rhythm. The head was normocephalic, with a circumference of 41 cm. The posterior fontanel was closed, the anterior fontanel 7 cm. in the largest diameter. The pupils reacted to light. The corneae were clear. Teeth had not erupted. There was mucus in both nares, the turbinates were reddened, and the ear drums were slightly injected. The left hemithorax was fuller than the right, without a precordial bulge. The chest was resonant to percussion. There was a prolonged expiratory phase, and early expiratory rales, as well as rhonchi on deep respiration throughout the chest. No cardiac murmurs were heard. A2 was greater than P2. The liver was palpable to the iliac crest; the spleen two fingerbreadths below the left costal margin. There were no herniae. No limitation of motion, clubbing or edema of the extremities was noted. The neurological examination was negative.

Laboratory data: Hemoglobin, 10 grams per cent; white blood cell count, 10,400 per cu. mm. with normal differential count; urine, specific gravity 1.034 with no abnormal findings; blood cultures were sterile; nasal cultures yielded staphylococcus aureus A; pharyngeal culture showed no pathogenic organisms; sickle cell preparation was negative; total serum protein was 6.7 grams per cent (albumin 4.4, globulin 2.3); cephalin flocculation test was negative; total serum bilirubin was 0.41 mgm. per cent; blood sugar, 77 mgms per cent.

Roentgenological examination of the chest showed enlargement of the heart in its transverse diameter (Figure 1). The electrocardiogram was unremarkable.

A clinical diagnosis of endocardial fibro-elastosis and bronchopneumonia was made.

Course: Under treatment with digoxin for 10 days, oxygen and vapor, and penicillin and chloromycetin for one week, the patient rapidly improved, and was discharged after 20 days in the hospital. Three days later she was readmitted because of increasing respiratory distress for the preceding two days. Her temperature was 39°C., the pulse rate was 160 per minute, and the respiratory rate was 68 per minute. She had extreme dyspnea and tachypnea. There were rhonchi throughout both lungs. The edge of the liver was again felt at the iliac crest. There was no peripheral edema. She was treated with intramuscular digitalis and oxygen, vapor and antibiotics. Within three hours after admission she died, at the age



FIG. 2. Situs viscerum, showing enlargement of the heart and the liver. The spleen is obscured by the dilated stomach.

of five months. Permission for autopsy excluded examination of the head. Post mortem examination was performed by Drs. Platt and Sicular, 12 hours after death.

Gross Examination

The body weighed 7000 grams and measured 61 cm. in length (normal). The external appearance conformed with that described in the clinical examination. Description of the internal organs will be limited to the pertinent findings. The scarcity of subcutaneous fat tissue contrasted with the seemingly well-nourished appearance of the body. There was no subcutaneous edema. The stomach was enormously dilated, and the lower border of the liver was seen 5 cm. below the right costal margin. There was marked enlargement of the transverse diameter of the heart (Figure 2).

The heart was uniformly enlarged weighing 86.5 grams (normal 29 grams). Except for petechiae the epicardium was normal. The foramen ovale and ductus arteriosus were closed. The left atrium was dilated and lined by diffusely thickened whitish endocardium. The pulmonary veins were dilated. The mitral ostium measured 6.5 cm. in circumference. There was slight nodular thickening of the mitral cusps along the line of closure, and of the chordae tendineae (Figure 3). The mural endocardium of the left ventricle was diffusely thickened and greyish-

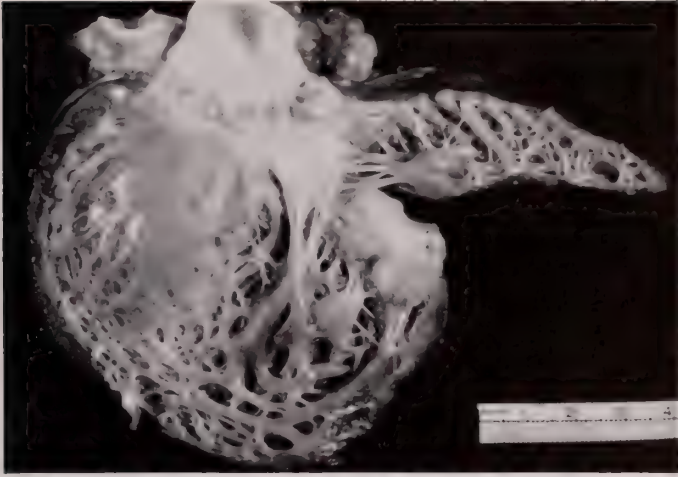


FIG. 3. Left ventricle showing hypertrophy and marked dilatation with diffuse endocardial fibrosis. Aortic valve grossly normal. Nodular thickening of posterior cusp of mitral valve.

white, with atrophy of the trabeculae carneae (Figure 3). The subendocardial portion of the myocardium was streaked with gray. Elsewhere the ventricular myocardium was red. The left ventricle was hypertrophied measuring 0.8 cm. in thickness, and considerably dilated (Figure 3). There was minimal thickening of the aortic valves. The aortic orifice measured 4 cm. in circumference. The right ventricle was dilated, and its wall measured 0.3 cm. in thickness. The circumference of the tricuspid orifice measured 6.5 cm., that of the pulmonic ostium 3.2 cm. The valve cusps were grossly normal. The right atrial and ventricular endocardium was thin, except for a small white patch over the interventricular septum. The aorta was elastic. The media appeared thickened, and there were white intimal patches or wrinkling, especially noticeable in the abdominal segment. The coronary ostia were patent, and the coronary arteries grossly normal. The main pulmonary artery showed no intimal changes.

The lungs were heavy weighing 156 grams (normal 73 grams). The right upper and lower lobes were non-crepitant, consolidated and dark red brown, while the remainder of the lungs were better aerated though hypocrepitant. There was venous congestion, especially of the left lung. A glary mucoid secretion was present in the main bronchi, as well as in their distal branches throughout both lungs. The hilar lymphnodes were reddened.

The liver was enlarged weighing 300 grams (normal 188 grams). It had a smooth thin capsule transmitting the mottled yellowish and red parenchyma. On section the lobular pattern appeared normal. There was no increase in consistency.

The spleen was enlarged to about twice the normal size weighing 33 grams (normal 16 grams). It was firm and had a smooth capsule. On the cut surface the splenic follicles were distinct.

Except for dilatation and subserosal petechiae of the stomach there were no

gross abnormalities of the digestive tract. The mesenteric lymphnodes were moderately enlarged, soft and pale tan.

The combined weight of the kidneys was 49 grams (normal). They showed moderate vascular engorgement.

There were no gross abnormalities of the thymus, pancreas, adrenal glands, thyroid, and internal genital organs.

Section of ribs showed that the costochondral junctions were not enlarged, the epiphyseal plates straight and regular. No deformity of the spine was noted. The periosteum did not appear thickened on gross inspection. The marrow was red, and there was abundant spongy bone.

Microscopic Examination

Heart. The left ventricular myocardium was uniformly hypertrophied. There were no vacuoles in the cytoplasm of the muscle fibers except in focal areas, especially corresponding to trabeculae carneae. These vacuoles could not be stained with Best's carmine, after fixation in 10 per cent formalin or absolute alcohol. In the posterior papillary muscle there was focal replacement of myocardial fibers by collagenous connective tissue which became increasingly hyalinized toward the site of attachment of the chorda tendinea. Embedded in this connective tissue were numerous large vacuolated cells, either singly, or in clumps or short rows (Figure 4). The shape of these cells, which varied from round or oval to polygonal, appeared to be determined by their spatial arrangement. The cytoplasm of many of these swollen cells remained completely unstained, or contained a very fine, faintly basophilic, fibrillar or granular material. Most of the cells had a small, dark eccentrically placed nucleus (Figures 4, 6). In focal areas there were accumulations of vacuolated cells unaccompanied by increased formation of collagenous fibers; these cells had larger and less pyknotic nuclei which were oval or kidney-shaped, and had a delicate nuclear membrane. In addition to these changes the papillary muscle contained small foci of early acute myocardial necrosis accompanied by leucocytic infiltration. Near the base of the interventricular septum there was some separation and focal atrophy of

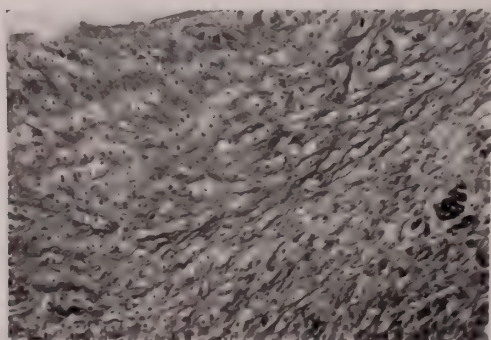


FIG. 4. Accumulation of vacuolated cells near the tip of a papillary muscle of the left ventricle, associated with wavy collagenous fibers. About 65 \times .

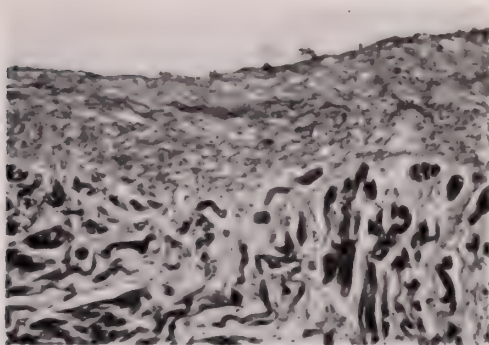


FIG. 5. Endocardial thickening in the left atrium, associated with vacuolated cells. Extension into underlying myocardium. About 65 \times .

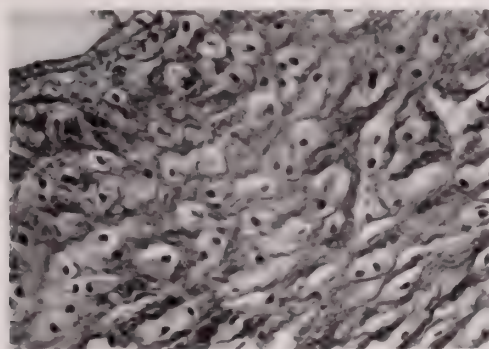


FIG. 6. Higher magnification of vacuolated cells at the base of the mitral valve, associated with an increase of collagenous fibers. About 250 \times .

muscle fibers by a delicate connective tissue containing vacuolated cells. Similar cells were encountered in the perivascular connective tissue septa, and in the adventitia of some of the myocardial bloodvessels which in places showed segmental infiltration with vacuolated cells under the intima and in the media which was attenuated by these cell accumulations. The myocardium of the right ventricle was not hypertrophied. The epicardium which was not thickened contained a few groups of ganglion cells which were normal. The most striking changes were present in the parietal endocardium of the left heart and in all the valves. The mural endocardium of the left atrium was most severely thickened (Figure 6), and to a slightly lesser extent that of the left ventricle, while the right ventricular endocardium only contained a localized patch of fibrosis. The endocardium consisted of abundant elastic and collagenous fibers and, embedded between these, a considerable number of vacuolated cells. In the ventricle the fibro-elastic thickening of the endocardium extended deeply into the recesses between the trabeculae carneae. Endocardial thickening was very striking in the region of the anuli fibrosi of the valves, and continued throughout the valves, even those that appeared normal to the naked eye. It was due mainly to the large number of swollen, vacuolated cells, together with a variable increase of

collagenous fibers and ground substance (Figure 6). In the valves there was no increase of elastic fibers. 0.1 per cent aqueous toluidin blue revealed faintly metachromatic granules in many of the cells. Metachromasia was almost completely abolished by incubation of sections with hyaluronidase for 20 minutes. Rinehart's colloidal iron technique brought into evidence distinct blue granules in many but not all of the swollen cells. Best's carmine stain for glycogen and the PAS technique gave negative results. The changes described in the valves extended into the root of the large vessels.

Blood vessels. The aorta was thickened due to patchy intimal proliferation of a delicate connective tissue in which vacuolated cells were embedded, many of which appeared somewhat shrunken. At the base of these patches the internal elastic membrane was split into multiple elastic fibrils. The media was thickened to a lesser extent due to the presence of vacuolated cells between the muscle and elastic fibers. Similar changes were found in the pulmonary artery. There was especially considerable thickening of the media due to infiltration with vacuolated cells. The coronary arteries showed segmental intimal proliferation of a delicate connective tissue, similar to that of the aortic intima. The internal elastic membrane was not altered. Focal subintimal proliferation was observed in a coronary vein. In the iliac arteries there was marked intimal thickening as in the aorta, while only slight intimal proliferation was present in branches of the mesenteric artery.

Lungs. There was marked diffuse venous congestion and edema, and numerous macrophages filled the air spaces. There were small foci of acute inflammation in the lung parenchyma, and a diffuse bronchitis with plugging of bronchi with mucus and epithelial cells. Bronchial cartilages, where seen, were normal. The intrapulmonic bloodvessels showed no intimal or medial alteration. There was acute inflammation of the trachea accompanied by marked mucous secretion. The pericartilagenous connective tissue was increased and contained vacuolated cells, especially in the zone of contact between the cartilage and fibrous tissue.

Liver. The liver cells were diffusely vacuolated, with a foamy cytoplasm and normal, often eccentrically placed nuclei (Figure 7). Frozen sections stained with Sudan IV showed a small amount of fat in the vacuolated cells, insufficient however, to account for the diffuse vacuolation of the parenchymal cells. Best's carmine stain for glycogen and the PAS reaction gave negative results. The Kupffer cells were swollen and vacuolated also, and difficult to distinguish from the liver cells in sections stained with hematoxylin and eosin. With Rinehart's stain they took on a blue coloration which was finely granular. In the liver cells blue granules could be recognized with difficulty. There was no increase of connective tissue. Venous congestion was present.

Spleen. The endothelial cells lining the sinusoids were enlarged and cuboidal, with a delicately vacuolated cytoplasm seen under oil immersion. The lymphfollicles were conspicuous due to reactive changes in their germinal centers. These contained occasional large vacuolated cells some of which were stained blue with the colloidal iron method, as were many of the littoral cells of the sinusoids. There were no foam cells in the intersinusoidal reticulum, and no increase of connective tissue.

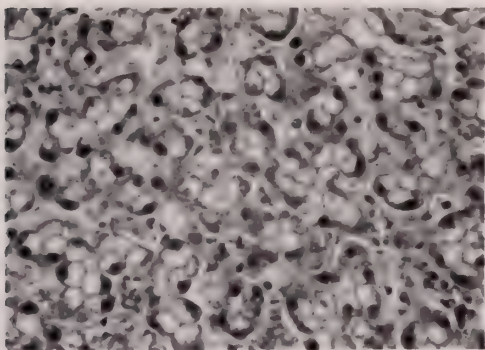


FIG. 7. Striking vacuolization of liver cells and Kupffer cells. About 250 \times .

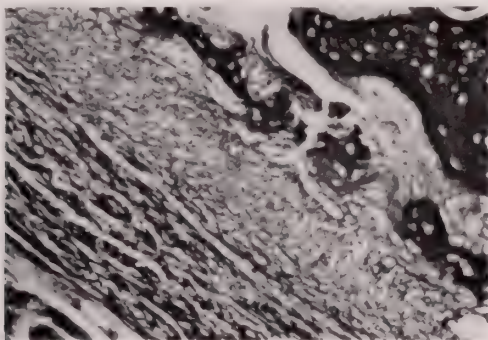


FIG. 8. Periosteal thickening of rib due to infiltration with vacuolated cells. About 65 \times .

Lymphatic tissue. The peribronchial and hilar lymphnodes of the lung showed congestion and hemorrhage, and many finely vacuolated cells lying free in the lymph sinuses. These cells were not seen in mesenteric and periaortic lymphnodes. Large round or polygonal cells were scattered through the thymic tissue; occasional large vacuolated cells were seen in the perivascular connective tissue.

Digestive tract. The ganglion cells of the autonomic plexus showed no abnormal vacuolization or ballooning. The submucosa of the intestine contained dense collagenous fibers and vacuolated cells, especially in the vicinity of blood vessels.

The remainder of the internal organs including the pancreas, kidney, adrenal glands, ovary, thyroid and parathyroid showed no parenchymal abnormalities, except for the presence of vacuolated cells in the connective tissue.

Bone. The width of the costal epiphyses was slightly increased due to a redundancy of the zone of proliferating cartilage on the inner aspect of the rib. The epiphyseal cartilage was permeated by a few tracts of delicate vascular connective tissue containing many vacuolated cells. There was no definite abnormality of endochondral ossification. However, distinct changes were observed in the periosteum and perichondrium. These were infiltrated by numerous vacuolated cells, particularly abundant in the cambium layer of the periosteum (Figure 8). The cortex of the shaft was thickened and consisted of bony islands divided by septa and lacunae filled with vascular connective tissue rich in vacuolated cells. The cortical bone was lined by numerous swollen osteo-

blasts some of which had a finely vacuolated cytoplasm. Islands of newly formed bone were seen in the altered subperiosteal connective tissue. The perichondrium was less severely thickened than the periosteum. There appeared to be a gradual blending of its vacuolated cells with the chondrocytes of the costal cartilage. The epiphyseal cartilage of an unselected vertebral body was normal, with active endochondral ossification. The bony trabeculae of the spongiosa were well formed. As in the ribs, there was thickening of the periosteum which contained vacuolated cells.

DISCUSSION

On the basis of the histological findings there is little doubt that diffuse endocardial sclerosis in this case was the result of abnormal storage of the type seen in gargoylism (Hurler's disease), unsuspected clinically and at the autopsy table. The term "gargoylism" focusses attention on the peculiar facies and the physical deformities encountered in most instances of the disease (10). This child did not have the monstrous appearance of classical gargoylism. Her somewhat broad features could be attributed to her race. The only previous report concerning a negro describes the classical clinical features of Hurler's disease (11). The normal height of our patient reflects the absence of chondrodystrophic changes. A roentgenological survey of the skeleton was not made. However, parts of the skeleton X-rayed incidental to examination of the chest, showed, upon later review, some broadening of the costal diaphyses (Figure 1), and cortical thickening of the humeral diaphyses. These findings are consistent with early roentgenological changes of gargoylism (12, 13). In view of the patient's heart disease enlargement of the liver was at first attributed to congestive heart failure.

The absence of gross skeletal deformities, abnormal facies, clinical hydrocephalus, corneal opacities and umbilical hernia places this case in the category of clinically atypical forms of gargoylism. One may assume that at the age of five months the disease process had not attained its full expression. Gargoylism is rarely recognized clinically under the age of six months, even in subjects who eventually manifest the complete classical picture of the disease. There are, however, *formes frustes* who may reach adult life without ever presenting the complete or typical syndrome. Among these are cases with normal corneae observed in males and thought to be associated with a sex-linked type of gargoylism (14, 15). In the absence of a slit-lamp examination and of histological study of the eyes in our case, early corneal changes cannot be ruled out with certainty.

The basic changes in the tissues in gargoylism appear to be very uniform, but their severity and distribution may vary considerably, especially with respect to the skeleton, the central nervous system and the cardiovascular apparatus. The implication of the heart and bloodvessels in the disease process has long been recognized. Clinically it is revealed by the frequency of "sudden death" or death in heart failure. The pathological changes of the cardiovascular system have been described (16-19), and reviewed in detail by Lindsay (9) who reported the case

of a 4½ months old boy whose clinical and post mortem findings resemble the case here described in almost every respect, except for the more protracted terminal phase of the illness in our patient. These two appear to be the youngest subjects known to have died as a result of severe cardiac involvement in gargoylism. Lindsay reports the ages at death from heart failure as ranging from 1 to 29 years (9). Since 1950 ten autopsied cases of gargoylism with some degree of cardiac and vascular involvement have been reported, their ages at death ranging from 28 months to 20 years (15, 18-24). Gross thickening of one or more cardiac valves was observed in the majority of these, and the typical microscopic changes were usually noted in the heart valves when subjected to histological examination. Vascular involvement, especially of the coronary arteries and the aorta was described even in instances where gross abnormalities were not noted. Fibrous thickening of the mural endocardium of one or more cardiac chambers has rarely been described in autopsy reports of gargoylism, and even when present, may have been slight, as in the cases of Magee (20) and Jelke (23), where it was observed only microscopically. There seems to be no concordance between the degree of valvular and mural endocardial involvement. This is exemplified by the case of a six year old boy with typical gargoylism, who had marked involvement of the mitral and aortic valves while the mural endocardium was normal (18). Diffuse endocardial thickening severe enough to suggest "endocardial sclerosis" in the absence of typical gross features of gargoylism, was present only in the infant reported by Lindsay (9) and the one described in this paper. In contrast to the experience of Lindsay, the heart in our case had diffuse involvement only of the left atrium and ventricle while the right ventricle only showed patchy fibrous endocardial thickening. The predominant involvement of the left side of the heart is not explained. It is very common in endocardial sclerosis of infancy not known to be associated with gargoylism. In the absence of conspicuous myocardial damage it appears unlikely that endocardial fibrosis be secondary to changes in the coronary vessels. Proliferation of elastic fibers in the thickened mural endocardium does not appear to be an exclusive feature of the "idiopathic" form of endocardial sclerosis. It is seen whenever proliferation of fibrous tissue occurs in the mural endocardium regardless of its cause (1, 25).

Cardiac involvement in gargoylism is not necessarily incompatible with prolonged life. Of the two brothers reported by Emanuel (19), one was still alive at the age of 26 years with clinical heart disease, while the other lived to be 20 years. Thus it seems that only occasionally may gargoylism present itself as a form of congenital heart disease with cardiomegaly, completely overshadowing the other manifestations of abnormal storage. Predominant involvement of one or a few organs may not be limited to the cardiovascular system, but has been observed in the brain and liver (26, 27). The recognition of the nature of the disorder in such individuals may be very difficult if not impossible, unless the observer is aware of the occurrence of atypical forms.

The structural alterations in gargoylism have been described in numerous case reports with post mortem studies. Basically, they consist of the appearance of enlarged, vacuolated cells in many organs and tissues of the body, not in-

frequently associated with an increase in fibrous tissue. On the basis of these morphological alterations, and of the familial nature of the disease, an inborn error of metabolism with abnormal storage has been suggested. The nature of the metabolic error is not yet fully understood. For many years gargoylism was thought of as a lipid storage disease because of the similarity of the changes in the central nervous system with those of amaurotic family idiocy (28). This concept was adhered to even though lipids could rarely be demonstrated in the swollen cells outside the central nervous system. Attention was first drawn to a non-lipid substance by the observation of de Lange et al (29) of large amounts of glycogen in a forme fruste of gargoylism. Later on, Smith et al (30) postulated a dysmetabolism of glycogen or an associated macromolecular substance, on the basis of similar findings in an atypical case of gargoylism. The water-solubility of the stored substance was noted in a classical case reported by one of us (16), and the lipid nature of the intracellular deposit was questioned also because of the resemblance of the storage phenomenon in gargoylism with that produced experimentally with high-molecular polysaccharides. Demonstration of polysaccharides in tissues was not successful, however. Lindsay et al (17) were the first to demonstrate a glycogen compound histochemically in typical cases of gargoylism.

Recent investigations have been concerned mainly with attempts at a more exact chemical identification of the stored material, which is still lacking. Henderson et al (18) could not demonstrate abnormal amounts of lipid or glycogen in liver tissue removed by biopsy from a typical case. A significant contribution was made by Brante (31) who observed a water-soluble substance in tissues from gargoylism, which had many properties of chondroitin-sulfuric acid. In view of this observation he characterized the disease as a mucopolysaccharidosis. Similar conclusions were reached by Dawson (21) and Jelke (23) on the basis of histochemical findings. The insolubility of the intracellular material in the brain is explained by a linkage of polysaccharides to cerebroside or phosphatids in the neurons. The puzzling relationship between chemically different substances stored in cells derived from different tissues, such as brain, mesenchymal derivatives, liver, blood cells, is discussed by Diezel (37). Postulating an enzymatic defect, each cell type is thought to accumulate a substance or combination of substances peculiar to its own metabolism, specific for each type of tissue. This challenging hypothesis would reconcile the seemingly contradictory results of histochemical and chemical investigations carried out on different organs. Bishton et al (24) for example, isolated a mixture of complex mucopolysaccharides containing mainly a heparin-like compound, from the liver but not from the spleen and brain of a typical case of Hurler's disease. The most detailed study of the chemical pathology of gargoylism so far has been reported by Uzman (33). He obtained two distinct fractions from spleen and liver of several cases: one a water-soluble glycolipid, the other a sulfonated polysaccharide. In view of the general involvement of tissues derived from mesenchyme he postulates an abnormality of structural polysaccharide metabolism. This view finds support in an observation by Meyer et al (34) who isolated chondroitin sulfate B from

the urine of a patient with gargoylism. This substance has been shown to be a major mucopolysaccharide component of skin, tendon, ligamentum nuchae and heart valves in the pig and ox (35). Its role in human connective tissue under normal and abnormal conditions has not yet been investigated. Meyer's observation opens a new avenue for biochemical investigation of gargoylism during life, as well as for biochemical and histochemical study of the tissues post mortem.

Because of the delayed recognition of the nature of the pathological process in our case, tissues were not preserved with a view to chemical or histochemical analysis. Fixation in formalin or alcohol dissolved a large part of the intracellular material. In view of previous negative results in the search for lipids in the visceral cells of gargoylism, staining for fat was limited to the liver which failed to reveal amounts of fat sufficient to account for the striking vacuolization of the liver cells. Glycogen could not be demonstrated in the heart, bloodvessels and liver. However, metachromasia with toluidin blue was observed in small amounts of intracellular material which evidently had not been completely dissolved by the fixative. Removal of metachromasia by hyaluronidase suggests that this material is of mucopolysaccharide nature. No metachromasia was seen in the liver cells or Kupffer cells. The colloidal iron technique after Rinehart (36) revealed blue granules within the swollen cells in sections of endocardium (especially the valves), spleen, perichondrium, periosteum, blood-vessels, and Kupffer cells. In the liver cells such granules could only be recognized with difficulty. The staining reaction which was most distinct and diffuse in the Kupffer cells, was not due to iron pigment. The significance of the difference in staining of liver cells and Kupffer cells is not understood, unless one assumes that the liver cells contain a compound which partially masks the reaction. This phenomenon has been pointed out by Craig (37) who found that the Hale colloidal iron reaction could be enhanced by lipid extraction in tissues from lipid storage diseases.

The histological and limited histochemical findings in this case suggest storage of partially insoluble compounds, possibly of mucopolysaccharide nature, predominantly in cells of mesenchymal derivation. Further histochemical studies are necessary for the identification of these substances, preferably after more appropriate methods of preservation of tissues.

SUMMARY AND CONCLUSIONS

A case of gargoylism in a five months old negro infant is described, presenting clinical features of acyanotic congenital heart disease with cardiomegaly, and gross anatomical findings of endocardial sclerosis. Structural alterations characteristic of gargoylism were present in histologic sections of the cardiovascular system, the liver, the spleen and lymphoid tissues, and the skeleton, with the exception of chondrodystrophic changes. The central nervous system and the eyes could not be examined.

The unusual features of this case are discussed in relation to the so-called formes frustes of gargoylism. The literature concerned with cardiovascular involvement, and the reported results of recent chemical and histochemical investigations are briefly reviewed.

Attention is called briefly to possibilities for clinical investigation of patients in whom the diagnosis of gargoylism might be considered in the absence of the characteristic clinical picture, as well as in typical cases. Instances of endocardial sclerosis should be included in such an investigation.

The metabolic disorder in gargoylism points to a mechanism by which endocardial fibrosis can be produced. The relationship of abnormal storage to fiber formation deserves further investigation. The findings in this case give support to the hypothesis offered by some investigators, that congenital endocardial sclerosis may be the result of a genetically determined metabolic disorder.

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FAT TISSUE GROWTHS

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Clear-cut differentiation of tumors into innocent and malignant species is not always feasible. Within nearly all histogenetic groups are tumors of intermediate or borderline behavior. This dilemma is particularly notable in the fat tissue growths.

Any attempt at orderly classification of the tumors of the adipose tissue is resisted by conflicting views on the origin and mode of growth of the fat cells, and their controversial relationship with other mesenchymal elements.

ORIGIN AND MODE OF GROWTH OF THE FAT CELL

Fat-forming cells are found in the human embryo in two different forms. One form is characterized by widely-spaced, spindle-shaped or stellate cells immersed in a mucoid intercellular substance (Fig. 1, A and B). The other form is contradistinguished by fat-laden cell groups, in adenoid lobules of a moruloid (mulberry) appearance (Fig. 1, C). These fatty lobules, generally known as "brown fat" because of their tan or light brown color, are confined to certain definite localities and make up well defined anatomical structures such as the perirenal fatty capsule, the suckling pad, and the interscapular fat bodies, etc. Unlike the "white adipose tissue" which may develop almost anywhere in the areolar connective tissue, brown fat arises in the embryo from specific *anlagen* which are constant in their distribution, and no new areas of brown fat appear in postnatal life. However, it should be emphasized that although "white adipose tissue" is almost universal in its distribution, it has a predilection for certain locations. This becomes most apparent during puberty and suggests that fat growth and distribution is influenced by local and systemic factors, endocrine and otherwise, the nature of which remains poorly understood.

The microscopic appearance of the brown fat is very different from that of ordinary fat. The cell of the ordinary fat is nearly spherical and usually contains a single large globule of lipid material enveloped by a very thin film of cytoplasm (unilocular fat cell). In contrast, the cell of brown adipose tissue is smaller in size, polygonal in shape, and generally contains several lipid droplets in a relatively abundant coarsely granular cytoplasm (multilocular fat cell).

Hibernating animals retain characteristic fat of both types throughout life, whereas, in the human multilocular brown fat cells are transformed into ordinary unilocular fat cells shortly before or after birth. These, however, under certain

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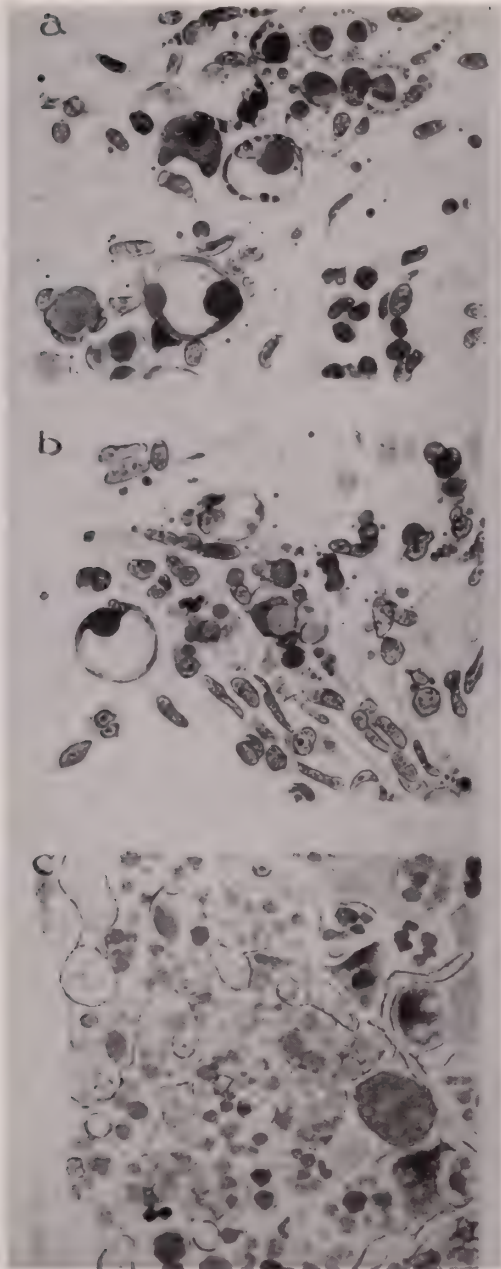


FIG. 1A. Early phases of fat cells formation in embryonal myxomatous subcutaneous tissue. Notice the transitional patterns from undifferentiated mesenchymal cells to spindle-shaped or rounded cells in which lipid droplets begin to accumulate (45 cm long human embryo, Sudan stain).

FIG. 1B. Similar stages of fat cell maturation in connective tissue adjacent to the Thymus gland (2 days old baby, Sudan stain).

FIG. 1C. Multilocular fat cells in adenoid arrangement, so-called brown fat (11-month old baby, perirenal region, Sudan stain). From the slide collection of Dr. P. Klemperer. Reprinted from the *Arch of Path.* (ref. 16).

conditions may revert to the original multilocular pattern and give rise to growths which mimic their embryonal characteristics. This may be interpreted as indicating that the two types of cells have a close genetic relationship and that the differences in appearance probably reflect phases of metabolic activity brought about by stimuli, the nature of which is not clear (1).

The old concept of the fat cell as a modified fibroblast which has assumed the function of fat storage is no longer accepted (2, 3). Substantial evidence from different sources indicates that the cell of the adipose tissue springs from a pluripotent undifferentiated mesenchymal cell in which fat globules are gradually deposited. According to this view, under local or general metabolic stimuli, the primitive mesenchymal cell of the connective tissue undergoes a series of changes, mainly characterized by the appearance of a spindle-shaped or stellate cell provided with long, coarse processes in which fat globules begin to be deposited. As this occurs this branched pre-adipose cell becomes rounded, its processes absorbed, and the nucleus displaced peripherally.

Ferrata's inclusion of the fat cell in the hemohistioblastic system (6), and Wassermann's almost identical concept that the fat cell originates from perivascular mesenchymal cells related to the reticulum (7) are substantiated by the presence of a pericellular reticulum and the ability to store vital dyes demonstrated by embryonal fat and to a lesser extent by mature fat cells (4, 5).

According to the traditional description, the adult adipose tissue consists of large cells containing a single fat globule encircled by a thin rim of protoplasm. However, according to Policard (9) the membrane of the fat cell is not of ectoplasmic origin but is contributed by the collagenous fibers of the fat tissue stroma. The fat particles floating in the blood stream would enter the cell by a physical process, conditioned by the colloidal status of the cell. From the study of transplants of adipose tissue, Marchand (8) has arrived at the same conclusion. Others (10, 11, 12) have brought out convincing evidence indicating that the wall of the fat cell is composed of both an outer membrane of reticular fibers and an inner protoplasmatic layer enclosing the nucleus at one point of the circumference. Nageotte and Guyon (13) have similarly depicted the fat cell "like a balloon suspended in its net", the net being composed of a thick network of interlacing precollagenous fibers, branching and anastomosing with one another, in the meshes of which lie the fat cell. Unless special stains are applied this meshwork cannot be seen (Fig. 2). However, it becomes visible in routine preparations upon formation of collagen fibers (14).

It is still debated whether or not mature adipose cells are capable of multiplying. Kölliker (15) has advocated this possibility. Instead Wassermann (7) favors the opinion that fat cell proliferation occurs through a reversion of the adult cell to the original pluripotent embryonal reticulum cell.

Observations on atrophic fat with regenerative activity, on fat under inflammatory stimulation and on early phases of an experimentally induced cancerous fat tissue growth (16, 17, 18) have led to concurrence that fat cell proliferation, both cancerous and noncancerous, takes place according to the same plan as that by which, in embryonal development, undifferentiated mesenchymal cells mature

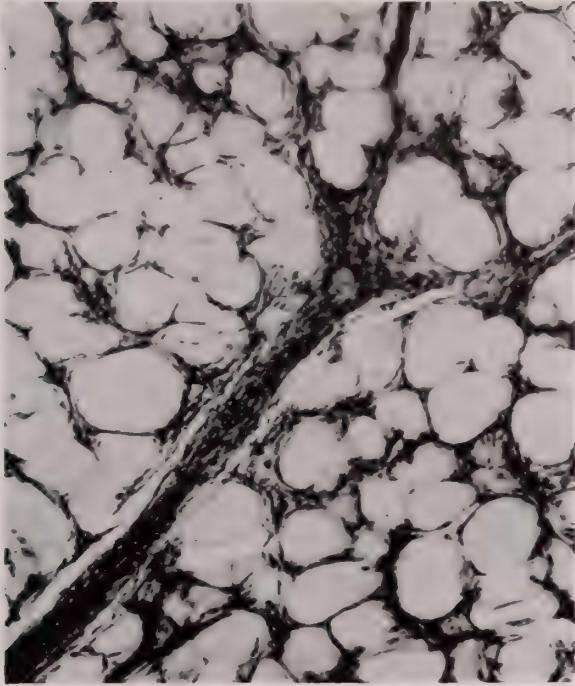


FIG. 2. Prominent pericellular reticulum of argentaffin fibers in mammary lipoma. Reprinted from the *Arch. of Path.* (ref. 14).

into fat cells. This is accomplished by the revival of dormant reticulo-endothelial cells embedded in the fat tissue (Fig. 3 and 4). Although it can be assumed that these pluripotent cells possess the ability to differentiate into fat cells wherever they occur, yet inborn or environmental factors must be postulated to explain regional differences in fat distribution with consistent racial patterns.

GENETIC RELATIONSHIP BETWEEN ADIPOSE TISSUE AND HEMATOPOIETIC TISSUE

The cyclic alternations between hematopoietic cells and fat cells within the marrow, and between lymphoid and adipose tissue, particularly in the lymph nodes and in the mesenteric fat, have been commented on by a number of investigators (16-23).

The genetic relationship between blood-forming and fat cells is implied by the comparable views of Ferrata (6) and Wassermann (7). The former included the fat cell with the hemohistioblastic system and the latter with the reticulo-endothelial system.

The embryonic appearance of hematic and lymphocytoid cells precedes or coincides with the formation of the primitive fat cells. Cioni (24) suggested that the formation of hematic cells is preceded by the differentiation of histiocytes into polyblastic cells.

Likewise a number of investigators have stressed the presence of a plasma-cell-like, or lymphocytoid cell within the embryonal connective tissue in which fat

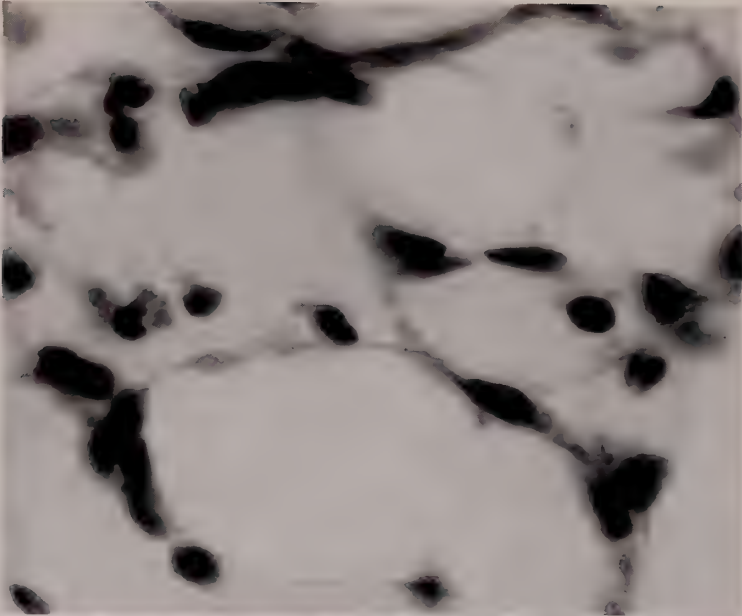


FIG. 3. Normal omental fat showing rounded or irregularly shaped histiocytic elements scattered in between the fat cells. H. & E. stain. 67-year old white male dying of pharyngeal carcinoma.

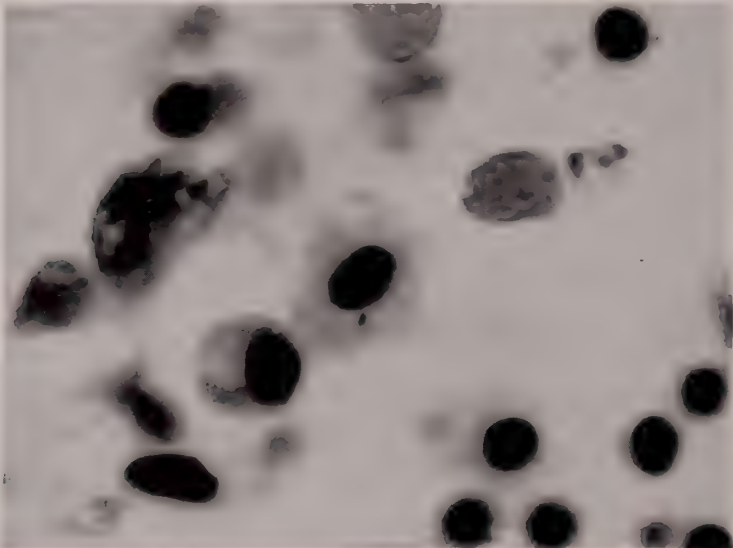


FIG. 4. Proliferation of lymphocytoid cells and of lipoblastic elements in atrophic periadrenal fat (61-year old man, with severe cachexia, secondary to generalized carcinomatosis). H. and E. stain.

cells later make their appearance. Waldeyer (25) theorized that the wandering plasma cell of connective tissue can be mobilized for fat storage. Bobritzky (26) and Poljakoff (27) expressed a similar opinion, and Geschickter (28) has suggested that these cells, resembling plasma cells, are the forerunners of the larger pre-adipose cells. Distinct transitional patterns between lymphocytoid cells, larger cells resembling plasma cells and fatty cells in various stages of development were observed by one of us (C.G.T.) in the fatty portion of a renal Wilms tumor (29), and comparable cellular forms in early developmental stages of an experimentally produced liposarcoma (18). Heterologous hematopoiesis within fat tissue is noted in a variety of conditions, including fat tissue growths best exemplified by the adrenal myelolipoma (30, 31).

HISTOCHEMICAL COMPOSITION OF NORMAL AND NEOPLASTIC FAT TISSUE

Recent biochemical investigations employing biological tracers have shown that stored lipids are not static reserves, but participate in many of the complex processes of lipid metabolism (32).

Fawcett (33), in a comparative histological and cytochemical study of brown and white adipose tissue found quantitative, but no qualitative, variations in composition.

In vitro metabolic studies have shown that brown fat of rats has a greater oxygen consumption (34), and glucose uptake (35) than white fat. *In vivo* metabolic studies have established that brown fat of rats has a greater rate of phosphorous turnover than white fat (36).

According to Menschik (37) brown fat contains less neutral fat, but more phospholipids and glucolipids, cholesterol, alpha-amino acid groups, water-soluble polysaccharides, cytochrome oxidase, amine oxidase and slightly more alpha-naphthol oxidase, than white fat.

Despite the similarity of constituents, the two tissues exhibit dissimilarities in their responses to certain endocrines (38, 39), vitamin deficiencies (40) and infectious agents (41).

Cramer (42) has suggested that brown fat belongs to the category of the endocrine glands. Sweet and Hoskins' (39) demonstration that extracts of brown fat from woodchucks possess androgenic activity nearly equal to that of bull testis supports this contention. However, Fawcett (33) has shown that the lipids of the brown fat fail to exhibit the birefringence and auto-fluorescence typical of the steroid hormones, that they give a negative Schultz reaction for cholesterol and that they do not react to the Ashbel-Seligman test for ketosteroids.

Failing adequate behavioristic explanation on structural or chemical basis, Wells (43) has suggested that lipoma fat differs from normal subcutaneous fat in metabolic activities. Kastle and Leavenhart (44) have shown that fat storage is dependent on the presence of a lipase. The absence of a lipase in the tumor fat might explain its inavailability to the host fat tissue.

Boeke (45) has demonstrated that sympathetic nerve fibers are present in fat cells, and that denervated fat tissue deposits contain more fat than normal deposits. Beznak and Hasch (46) have shown that there is an increase of adipose

tissue at the site of a sympathectomy, and that in emaciation fat persists longer at the site of denervation. The role of the sympathetic system in fat storage and metabolism deserves investigation.

Further discussion of hormonal influences would be repetitious. However, it is worth mentioning here that Geschickter (28) has succeeded in producing subcutaneous xantholipomatous growths in monkeys by injections of high concentrations of chorionic gonadotropin, obtained from pregnancy urine.

NEOPLASMA OF FAT TISSUE

Adipose tissue neoplasma can be divided into four main categories: a) benign; b) potentially malignant; c) malignant; and d) mixed. The last category includes benign and malignant forms in which there is associated neoplastic growth of fat storage cells with other mesenchymal cell types.

A. Benign

Lipoma, single or multiple, is the unquestioned representative of this category. The frequent presence of a tenuous capsule and the mature appearance of the cells, histologically and chemically indistinguishable from ordinary body fat, are clear exponents of its benignity.

Multiple fatty growths (lipomatosis) may arise in the subcutaneous tissues, in the internal cavities and in the deep organs. Excluding subcutaneous sites, the retroperitoneal and perirenal areas (47, 48, 49) and the intermuscular spaces (50, 51, 52) are the most frequent locations. Less frequently they are found in bones and joints or in the thoracic cavity in grape-like nodules along the intercostal spaces (53, 54, 55).

B. Potentially Malignant

It has been repeatedly proposed that liposarcomas may arise from supposedly benign fatty growths (47, 56, 57). Confirmation is difficult because fatty tumors often show intermingling of mature fat cells with immature lipoblasts, and as Stout (57) says, "One has no means of knowing whether or not this state of affairs existed from the onset." This seems particularly true for apparently benign, but frequently recurring, fatty growths, particularly those arising from the retroperitoneal and popliteal spaces, the thigh and the gluteal region (58, 59, 60). This suggests one of two main possibilities: either an outgrowth of fatty masses overlooked at operation, a point well stressed by von Wahrendorf (61) and Miller (62); or presence of nests of potentially cancerous embryonal cells harbored in the growth and missed through incomplete histologic study (63).

Detection of these nests of embryonic fat cells removes the tumor from the category of the innocent fat tissue growths. Local recurrence and eventual metastasis may follow incomplete excision. The non-infrequent presence of myxoid tissue containing spindle and stellate lipoblasts among mature fat cells has led to usage of terms such as myxolipoma, lipomyxoma, myxofibrolipoma and fibrolipoma, all with deceptive implications of benignancy.

Jaffé (60) named them lipoblastomas, but apparently was unaware of their

malignant tendencies. Since they differ both in structure and in behavior from the mature lipoma and carry malignant potentialities of growth, Stout (57) has properly suggested that they should be considered as "differentiated liposarcomas." However, a similar denomination, "adult liposarcoma", suggested by Ewing (64), has been used for many years to indicate the differentiated cell type of the unequivocal liposarcoma. Confusion may arise between Stout's differentiated liposarcoma, with latent cancerous potentialities and Ewing's adult liposarcoma which bears all the stigmata of a malignancy. Since the presence of nests of pre-adipose cells interspersed with far more numerous mature fat cells is the main feature of this potentially malignant growth the name embryonic lipoma ("lipome embryonnaire") proposed by Gricoureff (65) might be used to stress the embryonal cell component of this particular group of fat tissue growths.

Their unpredictable behavior is clearly demonstrated by the 18 cases reported by Geschickter (28). Nine showed one or more recurrences and 4 subsequently underwent malignant changes. A perirenal fatty growth recurred 4 times after excision within an 8-year period. Nevertheless, the removed tissues continued to display the misleading appearance of the original growth. Another tumor in the thigh recurred 5 times within 8 years, and 16 years after the first operation the patient died with metastasis. The morphologic aspects of this kind of growth are well illustrated by the following case:

Case 1

J. D. (Boston VAH), 41-year old white male. A rapidly-growing asymptomatic mass noted below right ear for one month was excised with capsule intact and consisted of a rounded, yellowish-gray, slightly gelatinous nodule 1.3 cm in diameter. Microscopic examination revealed mature fat cells of different sizes, with sparsely scattered or small groups of embryonal mesenchymal cells varying in size and shape. Some were rounded, resembling lymphocytes, others elongated, and still others stellate with irregular outlines and cytoplasmic processes. Nuclei were large and hyperchromatic with frequent nucleoli. No mitoses were seen. The cytoplasm of some of the largest cells contained several minute fatty droplets (Fig. 5, A and B).

Comment: This tumor was considered in the category of the embryonal lipomas. The growth was completely encapsulated and consisted almost entirely of mature fat cells. However, the presence of scattered preadipose and embryonal mesenchymal cells was interpreted as an indication of latent malignant potential. The pre-adipose cells were particularly prominent in proximity to blood channels, a location that in our experience is most likely to reveal their presence (Fig. 6). This finding supports Wassermann's (7) concept that fat cells originate from periadventitial mesenchymal cells related to the reticulum.

The multicentric counterpart of the solitary embryonal lipoma can be found in a rare condition that Goormaghtigh *et al* (66) in 1936 labelled "systemic multicentric lipoblastosis." Multiple, non-encapsulated fatty growths in the subcutaneous tissue, internal cavities, bones and deep organs are the main anatomical features. Clinical characteristics include frequent recurrences and long survival. As in the solitary embryonal lipoma, these growths are predominantly composed of mature fat cells with interspersed preadipose cells.

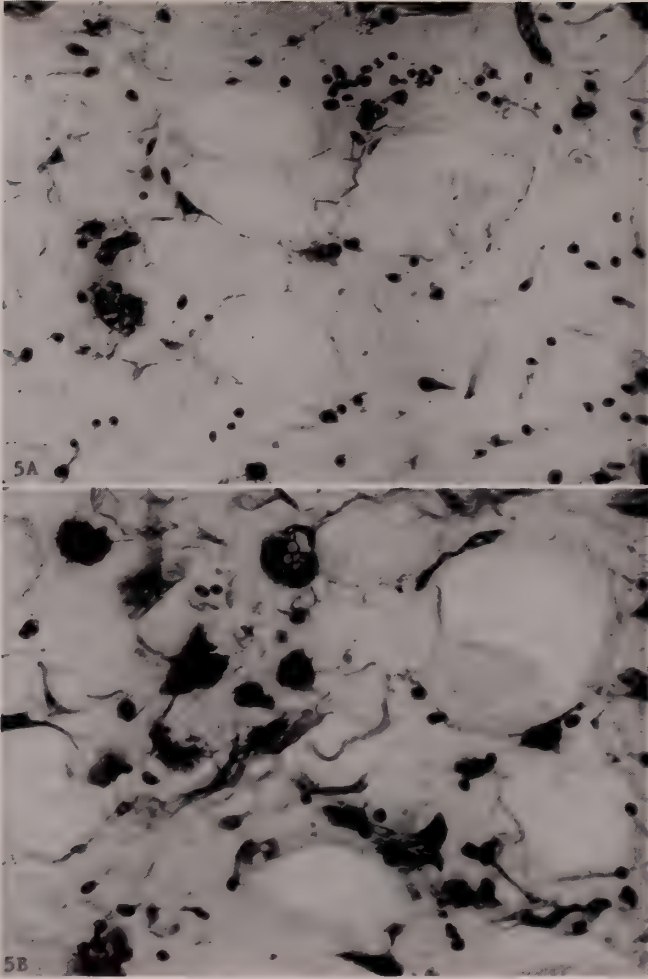


FIG. 5. *Embryonal lipoma* (Case 1, H. and E. stain).

FIG. 5A. Mature fat cells with interspersed undifferentiated mesenchymal cells and preadipose cells (lipoblasts).

FIG. 5B. High-power view of a nest of preadipose cells shown in Fig. 5A including immature mesenchymal cells and a large rounded lipoblast in which fat droplets begin to accumulate.

The distinctive features of this uncommon condition are well illustrated by the following case, made available to one of us (C.G.T.) by Dr. Klemperer and already reported elsewhere (16) in greater detail.

Case 2

Thirty-four year old white female. A popliteal tumor mass was removed and considered to be a benign lipoma. Six years later this mass recurred and a new fatty growth made its appearance in the neck. One year later a growth with the same characteristics developed in the abdominal wall and the popliteal mass recurred (second recurrence). In the following 2 years the patient developed paraplegia and a fatty mass was excised from the spinal extra-

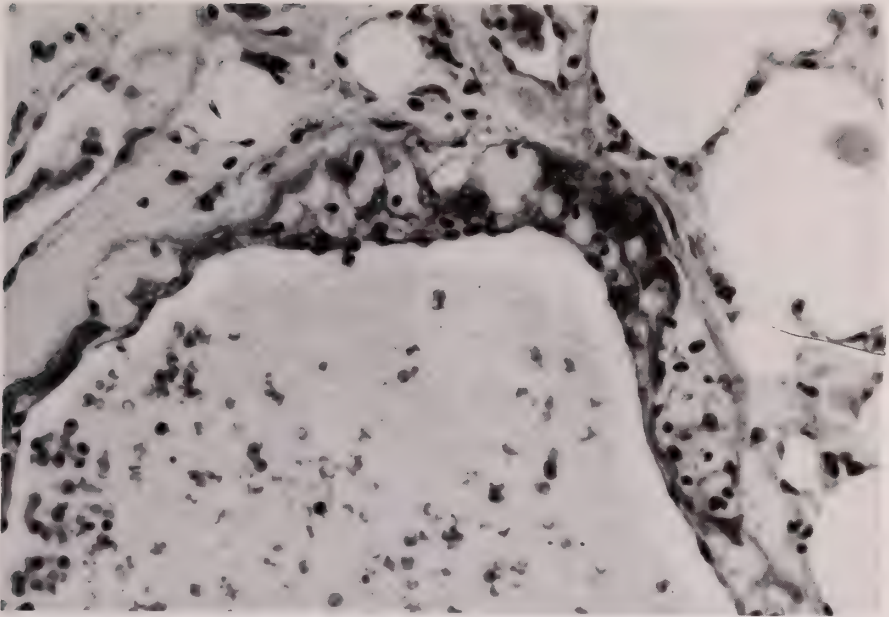


FIG. 6. *Embryonal lipoma* from another case showing perivascular lipoblastic cell proliferation suggesting origin of preadipose cells from periadventitial mesenchymal cells. H. and E. stain. Lipomatous mass in the right thigh of a 67-year old woman. Through the courtesy of Dr. B. Castleman, Mass. Gen. Hospital, Boston, Mass.

dural space. At this time the neck growth showed evidence of recurrence. After 3 months the extradural spinal mass recurred and numerous subcutaneous tissue tumors made their appearance. Death followed an attempt to remove the extradural recurrence 12 years after onset of the disease.

At post mortem numerous, non-encapsulated fat tissue growths were found in the subcutaneous tissue, neck, abdominal wall, thigh, popliteal space, extradural spinal space, thoracic cavity, adrenal region, mesentery, mesoappendix, transverse mesocolon and pelvis.

Comment: No evidence of cellular anarchy, no mitoses, and no invasion of blood or lymph channels were found in any of the numerous sections of the various fatty growths, which appeared to be mainly composed of adult fat cells and of less numerous undifferentiated mesenchymal cells, which occasionally showed progressive stages of maturation into fat cells (Fig. 7, A, B, and C).

Confronted with similar cases, Nienhuis (67) and Lubarsch (68) decided that the multiple fatty growths were metastatic; Siegmund (69) instead believed that both in his case and in the case of Lubarsch the multiple growths ("the tumoral nature of which is not clear") were independently originated. Goormaghtigh (66) favored this view, and I (C. G. T.) (16) interpreted my own case in the same fashion. Similar problems arise with cases reported by Hosemann and Lang (59), and Narr and Wells (54). Stout (57), commenting on these cases, favored the view of multiple independent growths, a question "of more than academic importance, for it has some bearing on the choice of treatment."

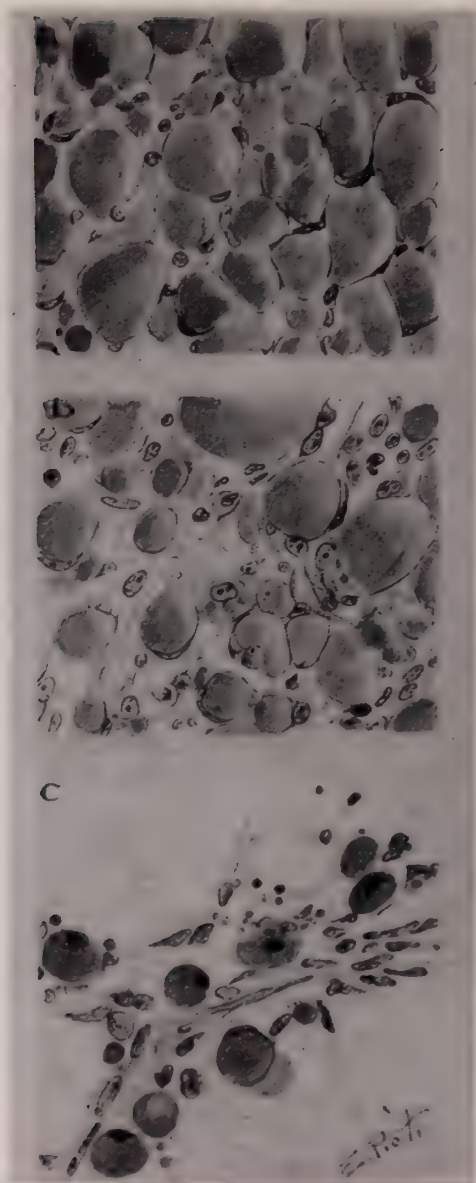


FIG. 7. *Systemic multicentric lipoblastosis* (Case 2).

FIG. 7A. Mature fat cells with interspersed occasional rounded or spindle-shaped mesenchymal cells. Primary popliteal masss diagnosed lipoma.

FIG. 7B. Mature fat cells and more numerous undifferentiated mesenchymal cells and preadipose cells. Mesenteric fatty mass, at post mortem.

FIG. 7C. A nest of preadipose cells showing transitional patterns from undifferentiated mesenchymal cells to lipoblastic elements. Fatty mass in the thoracic cavity at autopsy. Reprinted from the *Arch. of Path.* (ref. 16).

C. Malignant

Liposarcomas are characterized by disorderly proliferation of fat-storage cells, invasive power and metastasizing tendency.

It has been already indicated that fat-forming cells are found in embryonal life in two different forms. Both forms are reproduced in the cancerous growths of fat. This was detected by Ewing (64), hence classification into embryonal cell type (myxo-liposarcoma) and adult fat cell type, mirroring the two types of embryonal development of the fat tissue. This proposal has received due consideration in subsequent attempts at classification (28, 57, 70). However, as Stout has admonished (57), any subdivision of the malignant fat-forming tumors into rigid categories is doomed to failure. Transformation from one cytologic type to another type is not rare (71), and combinations of histologic types can be found in the same tumor. The fact that both myxoid and adenoid types may coexist in the same growth or alternatively appear in subsequent recurrences might indicate that the two forms of neoplasia probably spring from a common ancestral cell, capable of forming either or both.

In this connection the question arises: Do these different structural patterns reflect differences in the clinical course and response to treatment? If so, no effort should be neglected to improve our methods of anatomical classification.

The unpredictable behavior is clearly shown by the following two cases. One illustrates a markedly aggressive, rapidly growing mature cell, adenoid type of liposarcoma, and the other a slower-growing embryonal or myxoid type of liposarcoma terminally shifting into a mature cell type.

Case 3

H. R. (Boston VAH), 41-year old white male. In May 1954 a left popliteal mass, diagnosed adult cell type liposarcoma was removed and a mid-thigh amputation performed. In January 1955 the patient noticed swelling of the abdomen. Exploratory laparotomy disclosed a large non-resectable retroperitoneal mass which was biopsied. Biopsy revealed structure comparable to that of the previously-removed popliteal tumor. Shortly thereafter (February 1955) the patient developed respiratory difficulties and tumor nodules were disclosed in both lungs at x-ray examination. Two series of radiation treatment, one of 4500 r and the other of 2000 r were directed to the abdomen between February and May, and a third series of 2000 r was delivered in July. The treatments were followed by considerable improvement and diminution in size of the abdominal masses. In July another tumor mass was noted on the posterior neck, and in October the patient expired. Post mortem showed intra-abdominal, perivisceral, retroperitoneal and subcutaneous tumor masses with a total weight of 5250 gm. Tumor nodules were found also in the liver and lungs and the pulmonary veins showed gross evidence of invasion. The mediastinal nodes were involved, and in all localizations the neoplastic tissue displayed the characteristic pale yellow color of the adipose tissue.

Comment: The primary popliteal tumor and all growths examined at post mortem were composed of polyhedral or rounded cells, rather homogeneous in size and containing several small sudanophilic globules or a single large fat globule. Nuclei were small, centrally placed or eccentric. Mitosis was rare (Fig. 8). Despite this rather well-differentiated structure, the entire course was only 17 months. The massive invasion of the pulmonary veins and the detection of neoplastic cells in a mediastinal lymph node suggest metastasis rather than multicentric origin.

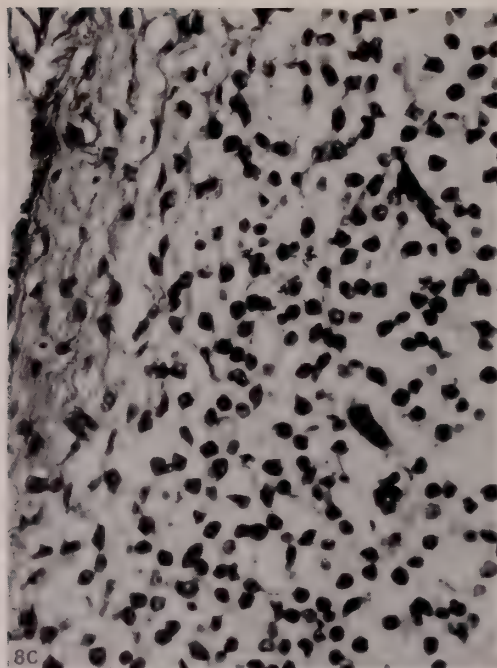


FIG. 8. *Mature cell liposarcoma* (Case 3). Lipoblasts in compact arrangement, in the absence of myxomatous stroma. From a subpleural metastatic nodule. H. and E. stain.

Radiation treatment effected temporary improvement. Comparable results have been recorded by others. However, reports on the effectiveness of radiotherapy on liposarcomas are in general discouraging. Both preoperative (64) and postoperative radiation have been recommended (73, 74), and the general impression is that small recurrent masses in accessible situations are more likely to respond than larger and deeper tumors.

Case 4

E. K., (Cushing and Boston VAH), 24-year old white male. In August 1949 a six by three inches, lobulated, soft-tissue mass was excised from the inner aspect of the right thigh and diagnosed myxoliposarcoma. Four years later, in March 1953, a soft, round, apparently movable mass appeared just anterior to the healed incision of the previously removed mass. The mass was excised and interpreted as recurrent myxoliposarcoma. Shortly after, in May, an abdominal mass was felt. It grew rapidly and in July of the same year a 2420 gm growth was removed from the mesentery and the retroperitoneal space. The intra-abdominal tumor proved also to be a myxoliposarcoma. By this time a new mass appeared in the right thigh (second recurrence) and was excised (January 1954). Five months later the patient expired, apparently of extensive atelectasis, produced by intra-abdominal tumor growth with upward displacement of the diaphragm. Post mortem showed 16,000 gm of myxomatous fatty nodules, involving the mesenteric fat, retroperitoneal space and visceral peritoneum of the abdominal organs. Similar nodules were found in the subcutaneous tissue of the right thigh and a single small nodule was seen in the anterior wall of the left ventricle of the heart.

Comment. From the first appearance of the mass in the thigh to the terminal event the process lasted 5 years. Microscopic examination of the masses removed

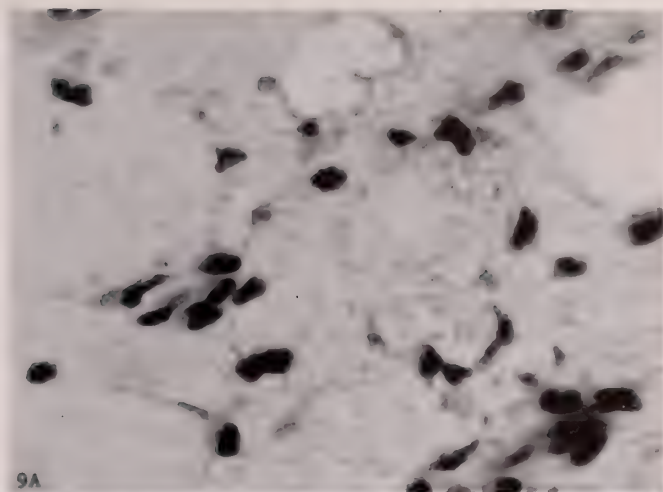


FIG. 9. *Myxoliposarcoma (embryonal liposarcoma)* (Case 4). Scanty lipoblastic cells immersed in myxomatous connective tissue. From the primary growth in the thigh diagnosed myxoliposarcoma. H. and E. stain.

during life and at post mortem showed that the tumor had undergone a remarkable transformation. The primary growth in the thigh and the masses subsequently removed were composed of a mucinous stroma with evenly scattered branched or stellate cells and less numerous cells with sudanophilic cytoplasmic droplets and larger mature fat cells (Fig. 9). The various tumor masses at post mortem revealed instead predominantly lipoblasts and mature fat cells, including typical signet-ring cells. A pale pink, slightly fibrillar stroma, which did not take the mucin stain, was still noticeable in areas, but less in amount than in the original primary growth. This suggests that during its course the tumor had undergone a shift in structure, from myxoid to adult cell type liposarcoma. Lymph nodes and blood and lymph channels failed to reveal invasion. Therefore, in this case the possibility may be entertained that the multiple fatty growths originated independently, as opposed to the concept of tumor metastasis.

D. Mixed Mesodermal Tumors with Fatty Component (Mesenchymoma)

The controversial relationship between adipose tissue and other mesenchymal tissues is mirrored by an uncommon category of growths composed of fat cells in association with other mesenchymal elements. The complexity of these growths has led to the necessity of identifying them by a special name. The designation of mesenchymoma (75) seems well chosen. Growths with these characteristics include both benign and malignant forms. The malignant variety is far more important. According to Stout's definition (76), malignant mesenchymomas are "tumors of the soft tissues of mesenchymal origin which are composed of tumor cells differentiating into two or more unrelated malignant forms." Since most of the liposarcomas have a fibroblastic component, tumors exhibiting this characteristic should not be included in the group. The same is true for the mixed mesodermal tumors in which fat tissue is present, but does not play an active

role in the growth. The natural history and morphologic aspects of this particular category are well illustrated by the following case.

Case 5

A. B., (Boston VAH), 28-year old white male. The patient was first seen in November 1949 for asymptomatic swelling of the abdomen of 9 months duration. At laparotomy 2270 gm of disseminated retroperitoneal nodular masses were removed. The pathological diagnosis was "myxo-lipoma with areas of sarcomatous degeneration." In January 1950, 620 gm of neoplastic tissue were removed from the right retroperitoneal space and pelvis. Microscopic examination showed, in addition to myxomatous and fatty elements, poorly differentiated striated muscle fibers, and the tumor was diagnosed "lipo-rhabdo-fibrosarcoma." Six months later the abdominal growth recurred and 3269 gm of tumor tissue were removed. Histological diagnosis was of "lipofibrosarcoma with areas of embryonic fat." In April 1951 the patient underwent his fourth laparotomy and 750 gm of neoplastic tissue were excised from several sites in the abdominal cavity. Pathological diagnosis was again "lipo-rhabdo-fibrosarcoma." Four years later, in April 1955, the intra-abdominal masses recurred and 3480 gm of tissue were removed from scattered areas within the peritoneal cavity. Of 13 sections examined, 8 showed myxomatous tissue with occasional large bizarre hyperchromatic nuclei and a scattering of immature fat cells. Three sections revealed relatively mature fat tissue, with large single droplets, or several smaller droplets, and occasional spindle-shaped or stellate cells, some of which contained a few sudanophilic cytoplasmic droplets. Two sections showed uneven admixture of the two types of tissue with rare multinucleated cells but no mitotic figures. The diagnosis at this time was "recurrent fibro-myxo-liposarcoma." Six months later, in October of the same year, 1412 gm of tissue with the same gross characteristics were removed from the pelvis, the right perirenal region and the mesentery. In the majority of the sections the bulk of the tumor seemed to have differentiated into fat tissue which could be classified merely as lipoma, and the atypical nuclei in the myxomatous element constituted the only malignant feature. Despite this relatively benign appearance, in March 1956, 6850 gm of tumor tissue were again removed from the abdominal cavity, together with the right kidney, whose ureter was blocked by external compression. Multiple sections revealed an irregular intermingling of fibromatous areas with rare swollen fibroblasts (Fig. 10A) of myxomatous connective tissue (Fig. 10B), and of fat tissue, mostly lipoblasts many of which contained minute sudanophilic fat droplets (Fig. 10C). Sharply demarcated areas of chondromatous tissue were also noticed (Fig. 10D). The cartilagenous cells ranged from poorly differentiated to mature, with a good deal of variation in the size of the cells, occasional large hyperchromatic nuclei and a few cells with two nuclei. The tumor was diagnosed "fibro-myxo-chondro-liposarcoma."

Comment: In a 7-year period this 28-year old man was operated upon 7 times and a total of 18,649 gms of tumor tissue were removed from his peritoneal cavity. Between operations he felt well and worked steadily as a machinist. When last seen he had no complaints, but in view of his past history further recurrences and eventually metastasis can be anticipated.

This case well illustrates the versatility of mesenchymal cells in neoplastic growth. Although the growths repeatedly obtained were predominantly composed of fatty and myxomatous tissues, in two occasions (second and fourth recurrence) tumoral striated muscle was recognized, and at the most recent recurrence chondromatous tissue was found. It is possible that both muscular and cartilagenous elements were overlooked in the primary growth; on the other hand, it cannot be ruled out that they developed later as the result of a

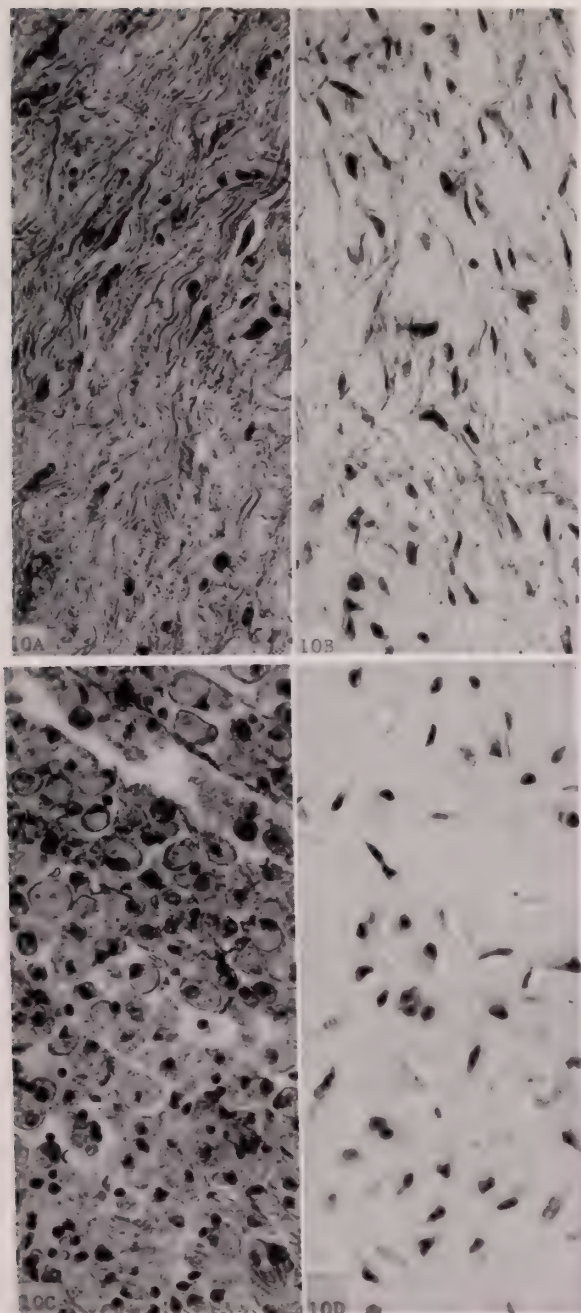


FIG. 10. *Malignant mesenchymoma with lipoblastic component* (Case 5).

FIG. 10A. Areas of fibrous connective tissue proliferation including swollen, atypical fibroblasts. From the intraabdominal mass removed at last intervention. H. and E. stain.

FIG. 10B. Myxomatous area.

FIG. 10C. Lipoblastic area.

FIG. 10D. Chondromatous area.

differentiation of primordial totipotent mesenchymal cells. Probably the process was initiated by a developmental disorder which resulted in a dysontogenetic type of growth.

CONCLUSIONS AND SUMMARY

1. Theories of origin and mode of growth of the fat cell are presented. Substantial evidence indicates that the cell of the adipose tissue springs from a pluripotent undifferentiated mesenchymal cell. The presence of a pericellular reticulum and the ability to store vital dyes substantiate the inclusion of the fat cell in the reticulo-endothelial system (hemohistioblastic system). The concept of the fat cell as a modified fibroblast is no longer acceptable.

2. The cyclic alternations between hematopoietic cells and fat cells within the marrow and to a lesser extent between lymphoid and adipose tissue, and the occasional finding of heterologous blood formation in the adipose tissue support the concept of a common ancestral relation for the fat cells and the cells of the lymph-hematopoietic tissue.

3. Pre-adipose cells are found in the human embryo in two different forms. One form is characterized by fat-laden cell groups in adenoid lobules (brown fat), and the other by widely-spaced, spindle shaped or stellate cells immersed in myxomatous connective tissue (white adipose tissue). As fat globules begin to be deposited these branched pre-adipose cells become rounded and their processes absorbed. Unlike the white adipose tissue which may develop almost anywhere, brown fat arises in the embryo from specific *anlagen* which are constant in their distribution and no new areas of brown fat appear in postnatal life. The microscopic appearance of this fat (multilocular fat cell) is very different from that of ordinary fat (unilocular fat cell). However, shortly before or after birth the multilocular fat cell of the brown fat turns into an ordinary unilocular fat cell and under certain conditions it may revert to the original multilocular pattern. This may be interpreted as indicating that the two cell types have common ancestral relations and that the differences in morphology merely reflect different phases of metabolic activity.

4. Evidence from various sources indicates that fat cell proliferation, both cancerous and noncancerous, takes place according to the same plan as that by which in embryonal development mesenchymal cells are brought to mature into fat cells. This is accomplished by the revival of dormant reticulo-endothelial cells embedded in the fat tissue. This does not exclude the possibility that proliferation of fat cells may occur under certain conditions through a subdivision of the nuclei of adult fat cells or through a return of adult fat cells to their embryonal stage, as suggested by others.

5. Tumoral growth of fat cells proceeds also according to a plan which does not differ fundamentally from that by which fat tissue develops in embryonal life. For practical purposes neoplasms of fat tissue can be divided into four main categories: a) benign; b) potentially malignant; c) malignant; and d) mixed, in the sense that growth of fat-bearing cells is associated with other types of mesenchymal cells similarly growing in tumoral fashion.

- a. Mature cell lipoma, either single or multiple, is the unquestioned representative of the benign category.
- b. Embryonal cell lipoma, either single (currently designated differentiated liposarcoma or lipoblastoma) or multiple (so-called systemic multicentric lipoblastosis) make up the potentially malignant group. Nests of preadipose cells interspersed with far more numerous mature fat cells are the main features of this type of growth which, upon failure of complete excision, may recur, infiltrate locally and perhaps spread to distant organs.
- c. Liposarcoma is the unequivocal exponent of the malignant category. The old subdivision into embryonal (myxoliposarcoma) and adult cell type is still justified on morphologic ground, with the understanding that both types can coexist and that transformation from one cytologic type to another type can take place. Since both structural patterns hold examples of slow and rapidly growing tumors, the two cell types do not seem to reflect a different clinical behavior.
- d. Mixed mesodermal growths with fat tissue component find proper classification among the mesenchymomas. They probably differ from pure lipoblastic neoplasias and represent developmental disorders resulting in a dysontogenetic type of growth.

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EOSINOPHILIC MENINGO-ENCEPHALITIS, WITH PREDOMINANTLY CEREBELLAR CHANGES CAUSED BY TRICHINELLA INFECTION

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It is well recognized in the voluminous literature of trichinosis (1) in man, that the clinical diagnosis of the sporadic form can be very difficult, particularly in the fulminating type ending fatally within a few days or from one to four weeks following infection. As Globus has stated, in discussing the paper of Most and Abeles (2) on *Trichinella* Encephalitis, the positive diagnosis is usually based on the history of ingesting infected meat, blood eosinophilia and a positive muscle biopsy. The absence of gastrointestinal symptoms, especially in mild infections, is well recognized. It has been observed also in severe infections and is stressed by Scott, Johnson and Holzman (3) in one of their cases with neurological and mental manifestations. Also, Skinners (4) called attention to the paucity of clinical signs of disease other than meningeal irritation, hemiplegia, aphasia, or some other localized neurological manifestations and to the absence of abnormal spinal fluid findings. Neurological changes of a focal type have been observed by Sheldon (5) in 17 per cent in an outbreak of trichiniasis as the presenting symptom, in the absence of pain or swelling of muscles.

While Frothingham (6) was the first to demonstrate part of a young trichina within a cellular infiltration in the brain of a man who had died during the fourth week of illness after a delirious state, our knowledge of the histopathologic changes in trichinella encephalitis is based on the detailed reports of Hassin and Diamond (7), Gamper and Gruber (8) and Most and Abeles (2). These authors, also, could demonstrate the trichinellae in the brain, usually in the center of small granulomatous nodules formed by glia cells, especially in the white matter. That chance in finding fairly intact parasites might play an important role can be inferred from two more recent reports. Betzendahl observed one single trichina in the brain, along with numerous fragments of the parasite (9); Schoepe (10), fragmented particles only.

In the sporadic case the source of infection might be obscured, local reactions of the recently infected intestinal tract minimal or absent, with *no* blood eosinophilia. The systemic invasion of the trichinellae, then, will lead to severe damage of the central nervous system before any symptom of muscle infestation is noticeable. Such cases pose difficult problems of diagnosis for all: the physician, the laboratory and the pathologist. In reflecting on the literature of the predominantly encephalitic type of trichinosis in man, one is hardly aware of the possibility that such fulminating infections might not be correctly diagnosed as to their parasitic cause, even if all organ systems can be studied by the pathologist. It is for this reason that a recent experience with a case of a rapidly progressing

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meningo-encephalitis will be recorded here, in which only after prolonged and often frustrating search of uncounted sections, a very few trichinellae could be demonstrated: in the brain, the leptomeninx, the laryngeal muscle and in the visceral pleura. But apart from these technical considerations which, we felt, should be emphasized, the gross and histologic findings in our case differ not inconsiderably from the few well documented cases of trichinella encephalitis in the literature.

CASE REPORT

C. H., a 6 year old white boy, was admitted to the Children's Hospital on 12-4-54 because of malaise, intermittent fever of one week's duration, lethargy and emesis for the past three days. Seven weeks preceding admission, he had developed a cough. Rales were present over the left lung and a presumptive diagnosis of pertussis was made by the family physician. Penicillin, 300,000 units daily, was injected intramuscularly for four days. The patient was also given Diatussin (extract of thyme and drosera) and Ambenyl (dihydrocodeinone bitartrate, bromodiphenylhydramine hydrochloride, ammonium chloride, potassium, quaiacolsulfonate and menthol). The tuberculin test was negative. To check a slight rise of the temperature, a syrup containing aureomycin was prescribed for about 10 days. The cough subsided after four weeks and the child was well for about one week thereafter, when the above-stated symptoms were noticed by the parents. There was fever of 103 degrees and stiffness of the neck. Penicillin, 400,000 units, was administered intramuscularly by the family physician on the day of admission to the hospital.

In 1952, he was seen in the Out-Patient Department because of insect bites with surrounding edema, for which Elixir Benadryl was prescribed. During the three succeeding summers, the child had severe urticaria. A sister of the child's mother has a strong allergy against coffee and tea. At the age of three years (in 1951) he had chickenpox. No one else at home was ill.

Examination at the time of admission revealed a well developed, well nourished, acutely ill, lethargic boy. Rectal temperature was 99.8, pulse 120, respirations 36 per minute and blood pressure 135/70 m.m. Hg. Eyes: nystagmus at rest; pupils round, regular and equal, reacting to light and accommodation; funduscopic, normal discs and vessels. Throat: injection of pharynx. The lungs were clear. Deep tendon reflexes equal and active; no Kernig's or Babinski sign.

Laboratory data

The urine had a specific gravity of 1.024, a negative reaction for sugar and albumin, a four-plus reaction for acetone, 2 RBC and 3 WBC per HPF.

Blood count: hemoglobin 12.5 Gm., RBC 4.8 million, WBC 21,800, with a differential of 70% filaments, 15% bands, 13% lymphocytes and 2% monocytes.

Nasopharyngeal culture grew rare colonies of *Staphylococcus aureus* non-hemolyticus; throat culture, very few colonies of the same microorganism and of *Streptococcus viridans* and *Streptococcus hemolyticus*. Cultures of blood and spinal fluid were sterile. On lumbar puncture, the initial pressure was 250 mm. water; there were 750 "lymphocytes" per cu. mm. in the spinal fluid; a stained smear for differential counting was not available; 4+ reaction on Pandy test; 71 mg. % glucose and 466 mg. % total protein with web formation.

X-rays of the chest showed a few scattered patches of bronchopneumonia at both bases.

The clinical impression on admission was encephalitis or meningitis. The child was given sulfisoxazole 1.0 Gm. stat and 0.5 Gm. q.6.h. intramuscularly, penicillin 400,000 units stat and b.i.d. intramuscularly, streptomycin 250 mg. stat and q.12.h. intramuscularly, isonicotinic acid hydraxide 60 mg. stat and q.6.h. and acetylsalicylic acid 0.3 Gm. q.4.h., as the fever had increased to over 102 degrees. Oral fluids were ordered and a polyionic solution was given by intravenous infusion.

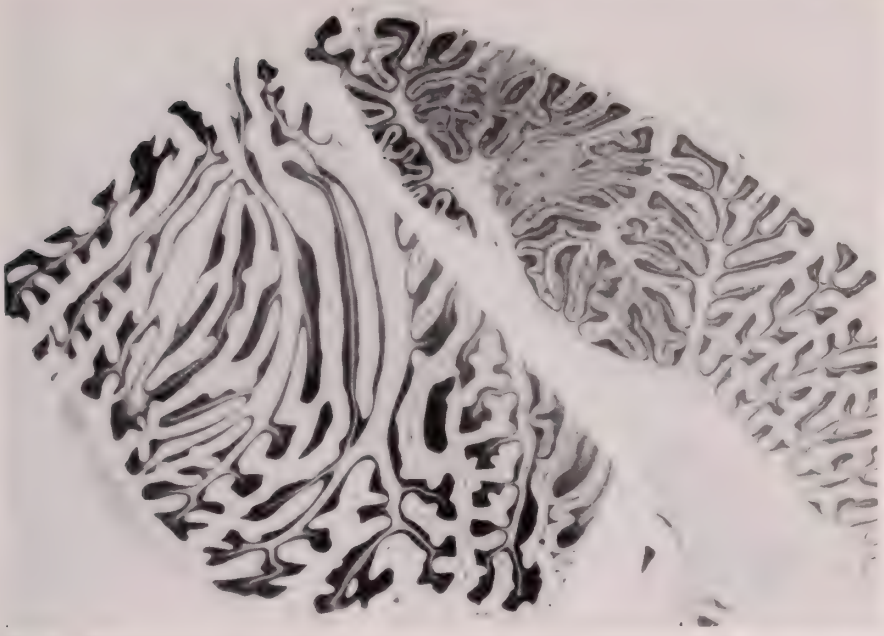


FIG. 1. Photograph of the celloidin section. To the right, heavily inflamed gyri from the right cerebellar hemisphere; to the left, less intense changes in gyri from the left hemisphere. Nissl.

On the morning following admission, the boy appeared more alert and was able to converse. By evening, however, he became lethargic and restless. Blood pressure, pulse and respirations remained the same as on admission. After midnight, his blood pressure fell to 60/0 mm. Hg., the pulse became weak and the patient expired at 4:50 a.m., less than 48 hours following admission.

Findings at autopsy

The autopsy was performed five hours after death. The pertinent post mortem findings were as follows:

The dura showed considerable distention due to uniform swelling of both cerebral hemispheres. When the tentorium is transected, the cerebellum appears under considerable pressure, particularly the right half. It is somewhat bulging over the midline, measuring 6 cm. in the right as against 5.2 cm. in the left transverse diameter. The markings of the swollen cerebellar gyri are indistinct (see figure 1.). The flattening of the gyri is most pronounced above the area of the right quadrangular, superior and inferior semilunar gyri. On the cut surface, gray and white matter appear very soft, though without actual liquefaction; in addition, the markings between cortex and white matter are distinctly blurred, particularly within the right hemisphere in the area of the above-mentioned gyri. Only after sectioning through the cerebellar substance it was noticed that the meninges are slightly thickened and hyperemic. When viewing the swollen right cerebellar hemisphere from the surface, one was somewhat reminded, by its peculiar discoloration, of a diffusely spreading glioma pressing upon the meninx.

This extreme swelling of the cerebellum had caused compression of the fourth ventricle and protrusion of the tonsils into the foramen magnum. Also, the floor of the third ventricle was somewhat bulging, but the aqueduct of Sylvius was not dilated. The middle ears, sphenoid and ethmoid sinuses were normal, as was the hypophysis.

The few other findings, worthy of note, included: a few petechiae in the mucosa of the hypopharynx and esophagus; recent small suffusions in the visceral pleurae, particularly along the interlobar surfaces; well aerated lungs, except for minimal atelectasis in the basal mediastinal portions of both lower lobes; larynx, trachea and bronchi free of abnormal secretions; a few petechiae in the mucosa of the stomach and some bile-stained, semi-fluid matter in the lumen of the small intestine and in ascending and transverse colon; thymus, all lymph node groups, heart, liver, pancreas, spleen, adrenal glands and kidneys of normal size and appearance, as was the bone marrow in sternum and vertebral column. Culture of the spinal fluid, post mortem, was again sterile.

In spite of the strange involvement of the cerebellum in this somewhat asymmetrical fashion, usually observed only in unilaterally expanding lesions such as abscesses or tumors, the anatomic impression as to the basic disease—influenced by the laboratory data and the clinical history—was in the direction of some inflammatory process rather than of a tumor.

It remained for the histologic analysis to clarify the nature of this peculiar swelling of the cerebellum. As one case of herpes encephalitis, proved by identification of the virus, had occurred a short time previously, a viral infection was thought of and material retained for virus studies. Rapid paraffin sections, however, disclosed a most intensive inflammation of the meninges and of the cerebellar tissue, with extraordinary predominance of eosinophilic leukocytes. It was felt, therefore, that we were apparently faced with an allergic inflammation, and virus studies were not carried through. Our next step consisted in histologic analysis of various striated muscles for trichinae. This proved completely negative in our preliminary search (muscles from the neck, ileolumbar region, diaphragm, larynx and pharyngeal wall were available, with negative results in all). No bacteria, fungi or parasites could be demonstrated in numerous paraffin sections of the cerebellum, brain stem and pallium containing the heavily inflamed meninges.

The fairly complete histologic examination revealed the extent of this acute meningo-encephalitic process, as it had affected various parts of the central nervous system and a few other organs in which no changes had been anticipated from their gross appearance.

Celloidin technique was used, with the following staining methods: Hematoxylin-Eosin, Nissl, Rasmussen-Power's modification of the Trichrome stain (for myelin sheaths), Gallego, Wright and Giemsa, Prussian blue and Sudan IV; in addition, Gram and Methylene blue stains on paraffin sections.

Histologic findings

Cerebellum: Extremely dense inflammatory infiltration of the leptomeninx, particularly marked in the sulci. The predominating cell type is the eosinophilic leukocyte, so that in the HE preparations, the meninges appear in a brilliant red color (Figure 6). Eosinophilic cells are also fairly numerous in the cerebellar cortex. The capillary walls are distinctly swollen, their endothelial nuclei very prominent. Other cells forming the exudate include lymphocytes, mononuclears, macrophages, neutrophilic leukocytes and a few plasma cells and peri-adventitial histiocytes. Some subarachnoid spaces on the surface are distended by a protein-rich fluid with a typical fibrinous network, containing some nuclear debris, but only a few preserved round cells, eosinophiles and disintegrating leukocytes. Some sulci, filled with thick masses of cellular exudate, appear broader than the bordering cortex and there is most massive infiltration of the walls and perivascular spaces of veins and capillaries in gray and white matter. Within these massive cuffs, lymphocytes are more predominant. In areas with the extremely dense meningeal infiltrations on the surface and within sulci, the architecture of the cerebellar cortex and medulla is markedly blurred (Figures 2 and 3). In the heavily involved cerebellar cortex only a faint irregular line of the original granular layer has remained. Within the molecular zone, there is a dense mixture of proliferating glial cells, lymphocytes and numerous eosinophilic leukocytes

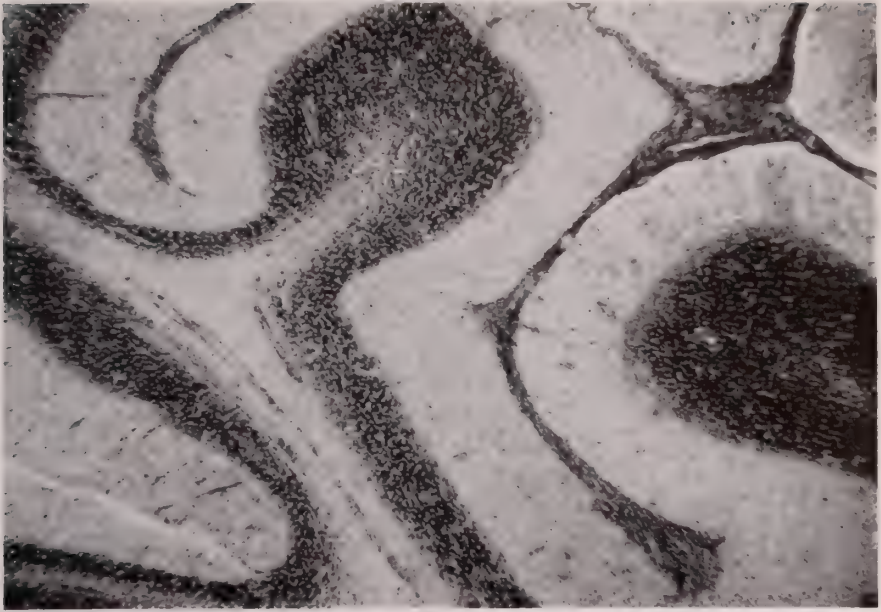


FIG. 2. Cerebellar gyri with uniform diffuse meningo-encephalitic changes. Note the marked cellularity throughout the molecular zone and the prominent cuffs in cortex and white matter. Nissl.

between the heavily inflamed capillaries and veins, bordered by thick cellular mantles. The Purkinje's cells have completely vanished in such areas (Figure 2).

There are massive inflammatory infiltrations also around the veins in the white matter of the cerebellum, including the area of the dentate nucleus. The cuffs about these vessel walls, as in the cortex, are so dense that they exceed the diameter of the distended lumen. In contrast, the arteries in the meninges are not, or only slightly, infiltrated; rarely a few leukocytes are seen within the wall of arterial capillaries.

In the choroid plexus relatively few infiltrations are seen in the mesenchymal stalk, consisting of eosinophiles and lymphocytes; the epithelium is intact.

The Nissl preparations show the fulminating inflammatory process very clearly, particularly in the deeper gyri. In some of these, only the proliferating glial cell layer of Bergmann is denoting the original delineation of molecular and granular zone. No trace of the Purkinje cells is left (Figure 4). In other areas, where the changes are somewhat less marked, a few Purkinje cells have remained, with rounded contours and all signs of severe ischemic damage ("homogenous"), and with various degrees of "glia-strauchwerk" formation (figure 5). In many such gyri, the proliferating glial cells have given the molecular zone a uniform dense cellular appearance. The majority of them, frequently proliferating in a streaming fashion, seem to originate from the Bergmann layer. In addition, there are numerous young astrocytic glial cells seen, with round or rod-shaped nuclei, lying perpendicularly to the proliferating Bergmann cells. Thus, in the densely cellular areas of the molecular zone, most of the glial elements correspond to the young fiber-producing astrocyte-type. Here, the microglia is less conspicuous than along the outer border underneath the meninges. Degenerating Purkinje's cells are surrounded by neuronophagic glial cells of the ameboid type.

In the white matter, there is distinct edema. Close to the perivenous cuffs, a few proliferating protoplasmatic glial cells are seen, forming the well known "rasen".

In sections stained with Sudan IV, there are fairly numerous macrophages seen within

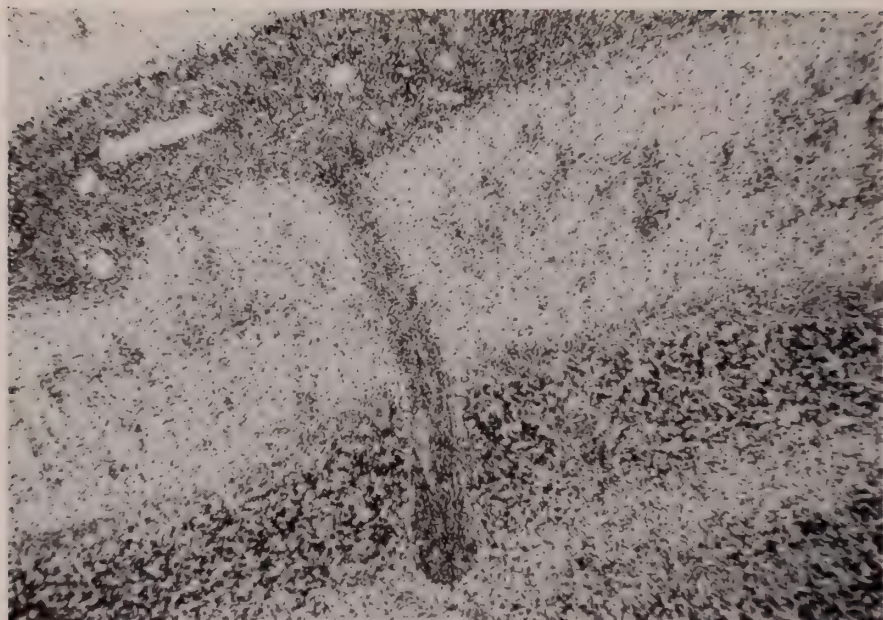


FIG. 3. Most severely inflamed cerebellar gyrus with massive meningeal infiltrates (upper, left and center). Note complete absence of Purkinje cells. Nissl.

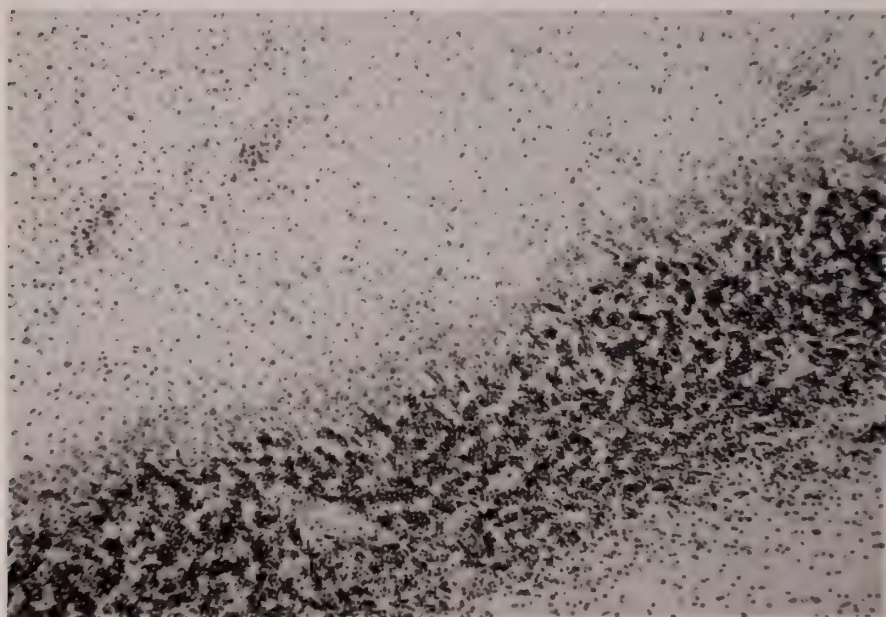


FIG. 4. Cerebellar cortex with molecular and granular cell layer from a severely damaged gyrus. Detailed description in text. Nissl.



FIG. 5. Cerebellar cortex with typical change from moderate "strauchwerk" formation on the left, to dense glia cell proliferation on the right. The small dark fragmented nuclei in the molecular zone are eosinophilic cells. Note the pale rounded bodies of a few Purkinje cells. Nissl.

the meningitic exudate, filled with small, distinctly staining granules and globules, usually close to capillary walls, and also within the perivascular cuffs in the cerebellar cortex and medulla. The heavily infiltrated areas of the molecular zone show in almost all proliferating glia cells fat-staining granules within their cytoplasm. This reaction is not seen in the molecular zone, where the Purkinje cell layer is intact or only slightly damaged. The fat stains show, in addition, very distinct perivascular edema about small veins in the white matter. Also, in areas where no fat granular cells are seen within or around the infiltrated blood vessels, neither the fat stain nor the myelin sheath stain reveal any clear evidence of demyelination.

Dense meningitic exudate is present also about the cerebral cortex, brain stem and spinal cord.

Inflammatory changes within the brain substance, however, are less marked. In the cerebral cortex, there are some meningo-encephalitic changes, restricted to the outer layers, more distinct in the frontal and motor area than in the occipital, temporal and parietal lobes. They seem to depend primarily on the heavy infiltration of the meninges and of the connecting venous blood vessels in the outer part of the cortex. Surrounding the inflamed capillary venules in the second and third layer are distinct proliferations of microglia (figures 7 and 8). Eosinophilic cells in the meninges of the cerebral cortex are just as prominent as around the cerebellum. Apart from these comparatively slight and focal changes, conditioned by perivascular cuffings of a few ill-defined pericapillary infiltrations in the second layer, there is no disturbance of the architecture in the cortex of the pallium. In the hippocampal area, the inflammatory process is restricted to a few intramural and perivascular cuffings, mostly in the white matter or close to the ependyma.

Very small pericapillary lymphocytic infiltrations were also seen between the pontine nuclei, somewhat more marked in the medulla, between the nerve cells of the cuneate nuclei (figure 9), and in the medial portions of the thalamus (figure 10). A few small perivascular

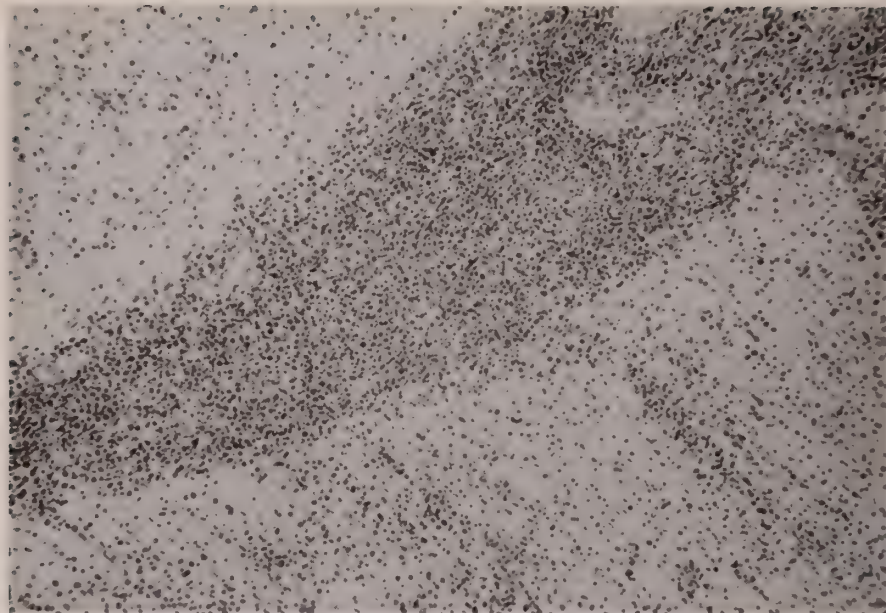


FIG. 6. Cerebellar cortex with a deep sulcus and molecular zones at both sides. Very numerous eosinophilic leukocytes in leptomeninx, within the sulcus and in the molecular zone. Hem.Eos.



FIG. 7. Meningitic and superficial cortical infiltrates in first and second layers. Frontal area. Note marked proliferation of microglia cells. Nissl.

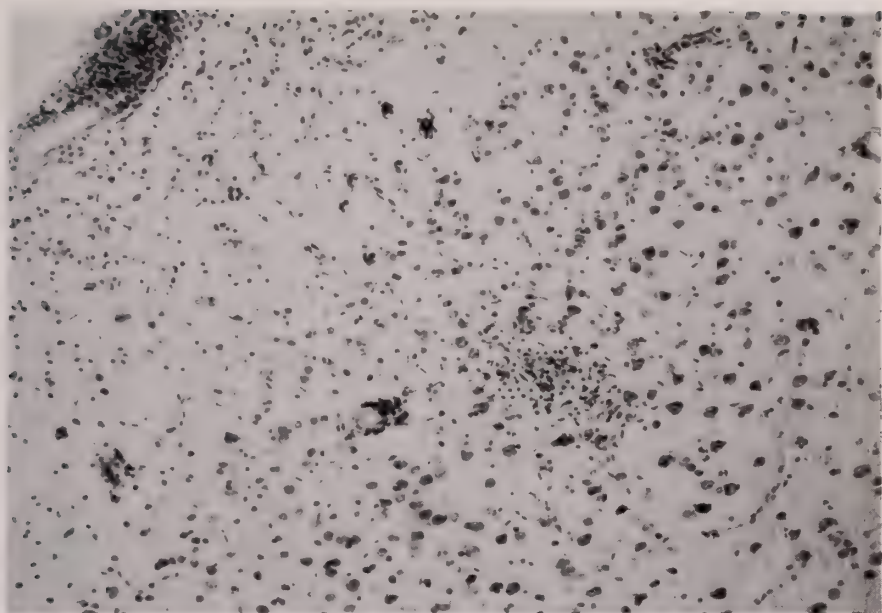


FIG. 8. Single encephalitic infiltrate in third layer; distinct microglia reaction in outer layers, underneath the meningeal infiltrate. Frontal area. Nissl.

lymphocytic infiltrates are present, also in the putamen and close to the ependyma of the fourth ventricle.

Only the upper cervical segments of the spinal cord were examined. No inflammatory or degenerative changes are seen in gray and white matter, in spite of distinct meningeal involvement.

The white matter of the cerebrum shows only a few small perivenous infiltrations, especially near the ependyma of the lateral ventricles. In the cerebellum, such perivenous cellular infiltrations are much more marked, particularly also in the deep white matter, including the area of the dentate nucleus.

The only hemorrhage encountered was of recent capillary type and of minute extent about a distinct inflammatory reaction in the medial portion of the thalamus. The Prussian blue reaction for stainable iron pigment was negative in *all* sections.

Stomach: Distinct edema, especially marked in submucosa and subserosa; the submucosal veins are surrounded by leukocytes, lymphocytes and very few eosinophils. Similar infiltrates are seen about numerous capillaries, with recent hemorrhages, in the tunica propria. Figure 11 demonstrates one of the perivenous infiltrations within the edematous submucosa, which were usually seen underneath the protruding plicae.

Hypopharynx and Upper Esophagus: Comparatively sparse infiltrations by leukocytes and lymphocytes, with few eosinophilic cells within the edematous tunica propria.

Jejunum: Distinct acute inflammatory changes, restricted to the mucosa, with dense infiltration throughout the stroma of the villi by numerous eosinophilic cells and leukocytes. There is distinct hyperemia of the mucosal capillaries and marked mucous secretion.

Lower Ileum: Marked hyperemia in mucosa and submucosa with prominent lymph follicles and conspicuous edema of the germinal centers, the reticulum of which is infiltrated by leukocytes. Along the borders of these aggregated lymph follicles, facing the submucosa and between the solitary individual lymph nodules, there are distinct leukocytic infiltrations along the capillaries. The edema of the submucosa in some areas is as marked as in the

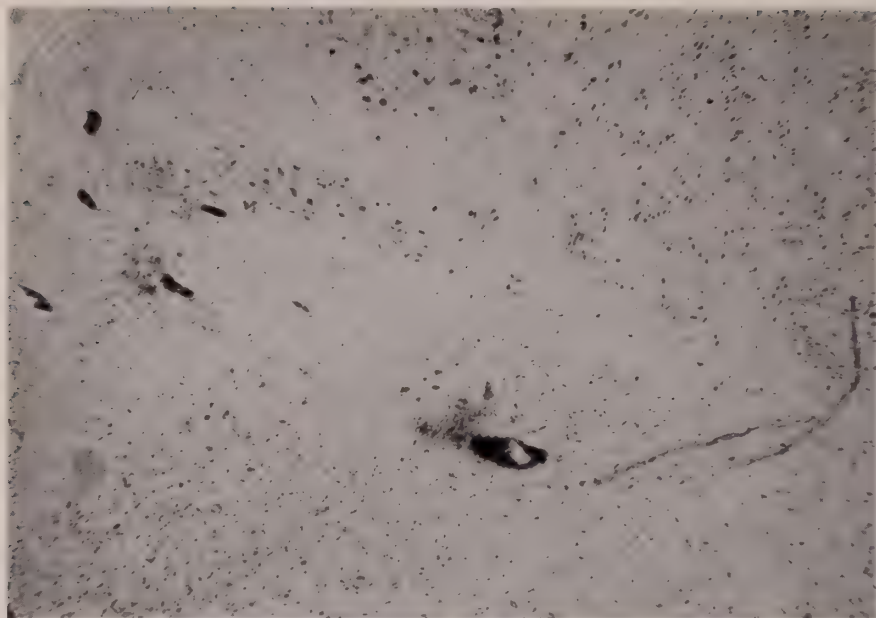


FIG. 9. Thick "cuffings" in oblongated medulla. Nissl.

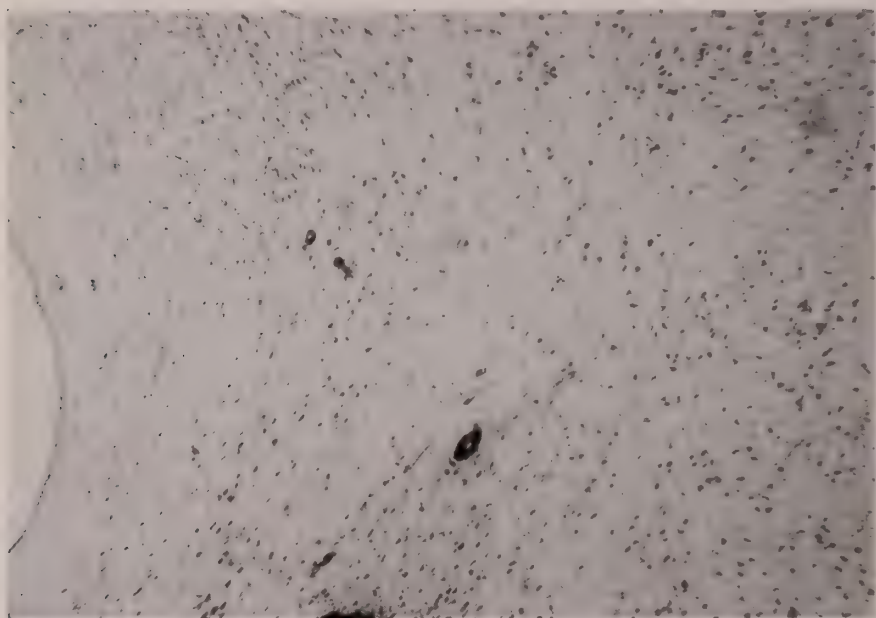


FIG. 10. Dense perivenous infiltrates in thalamus, near the ependyma. Nissl.

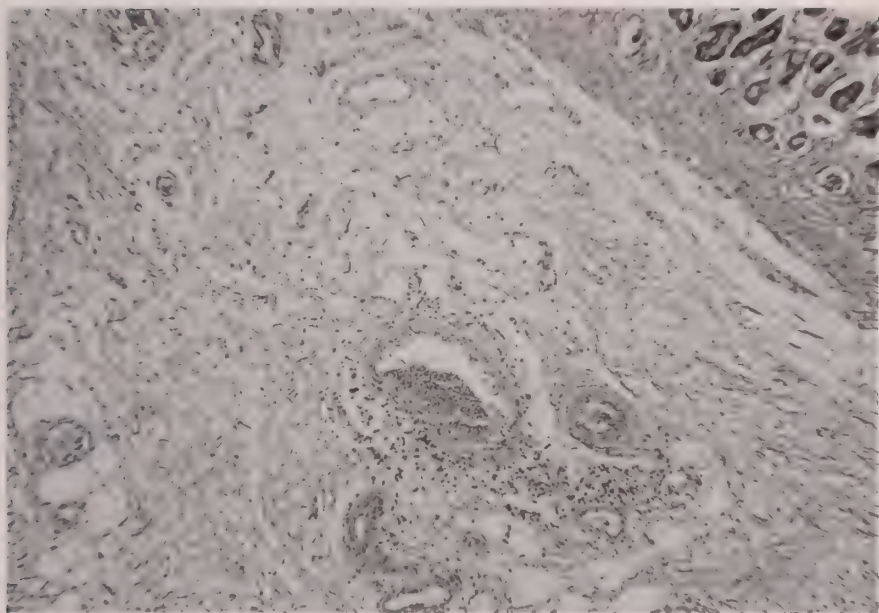


FIG. 11. Stomach; edematous submucosa with part of mucosa in right upper corner. Description in text. Hem.Eos.

stomach. There are numerous leukocytes and eosinophilic cells within the edematous stroma of the villi (figure 12).

Colon: Similar changes of a somewhat lesser degree; infiltration by leukocytes and numerous eosinophils is present. There is, however, no edema.

Liver: Infiltrations by leukocytes and eosinophils within periportal triades, including some of their smaller ramifications. The walls of arteries and arterioles are intact. The infiltrations are largely seen around the smaller branches of the portal vein.

Spleen: The reticulum meshes of the red pulp are fairly uniformly filled with leukocytes and eosinophilic cells. The picture is not unlike that of a recent inflammatory splenic reaction. These changes are here and there encroaching upon the periphery of the Malpighian follicles. The arteries are intact.

Mesenteric Lymph Nodes: Slight edema of the medullary portions and capsule, but no inflammatory exudate.

Larynx: Slight edema of the mucosa, considerable mucous secretion within the glands, but only very slight infiltrations of the mucosa by leukocytes and lymphocytes. The pyriform sinus shows distinct edema.

Lung: Minimal infiltration in the outer walls of small bronchi outside of their muscle coat, by few leukocytes and lymphocytes and about some surrounding peribronchial alveoli; edema around the concomitant pulmonary arteries and in the pleura.

Heart: Left ventricle—Edema of the endocardium and of the adventitia of some small arteries, with but rare infiltrates of a few histocytes. Right ventricle—Clusters of recent thrombi, consisting largely of fibrin and leukocytes adherent to the endocardium and completely blending with the heart wall, as if forming part of it, though apparently free of organizing cells and capillaries. There are no eosinophiles seen within these white thrombi.

Pituitary: Very dense eosinophilic and neutrophilic infiltrations in the leptomeninx about the anterior lobe.

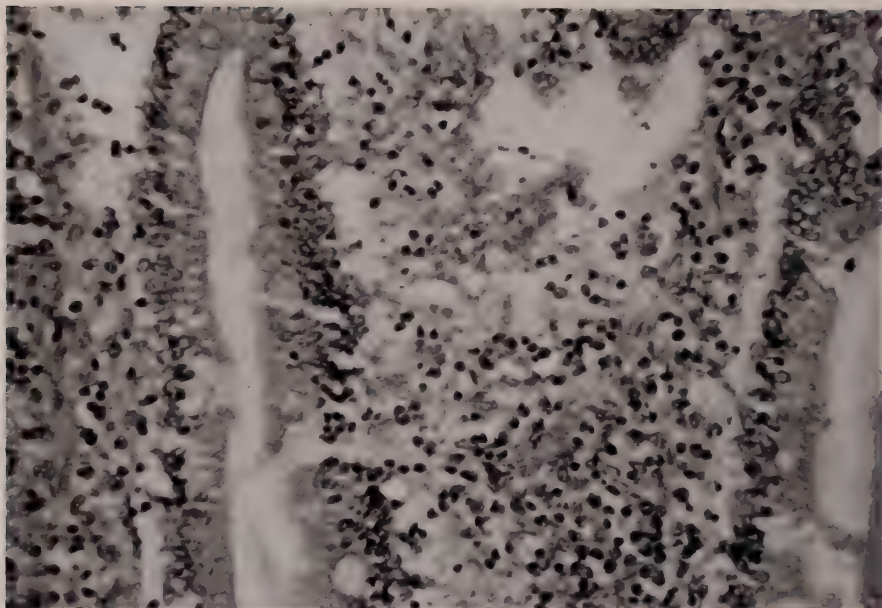


FIG. 12. Ileum; villi with marked edema and acute cellular infiltrates. Description in text. Hem.Eos.

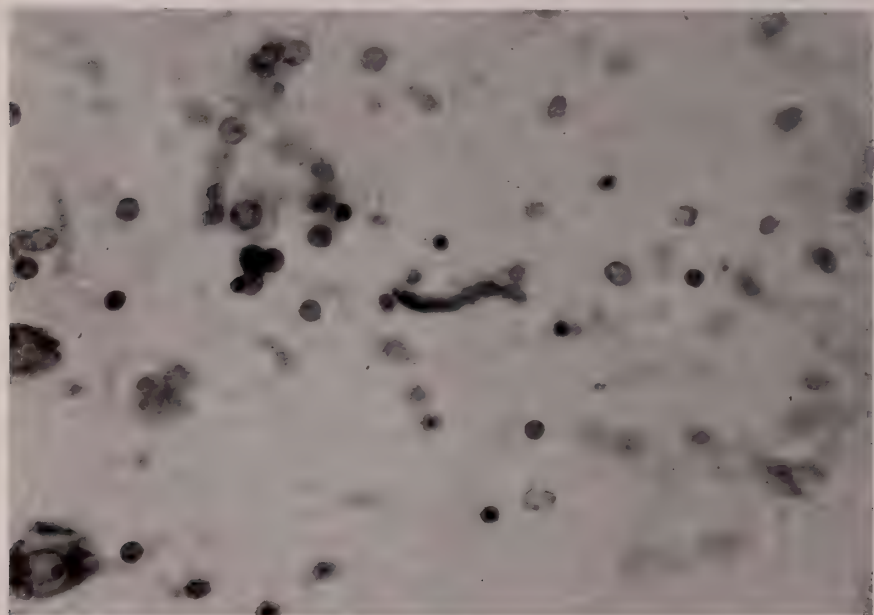


FIG. 13. Part of a single trichinella. Disintegrating nerve cell to the left and above the parasite. Nissl.

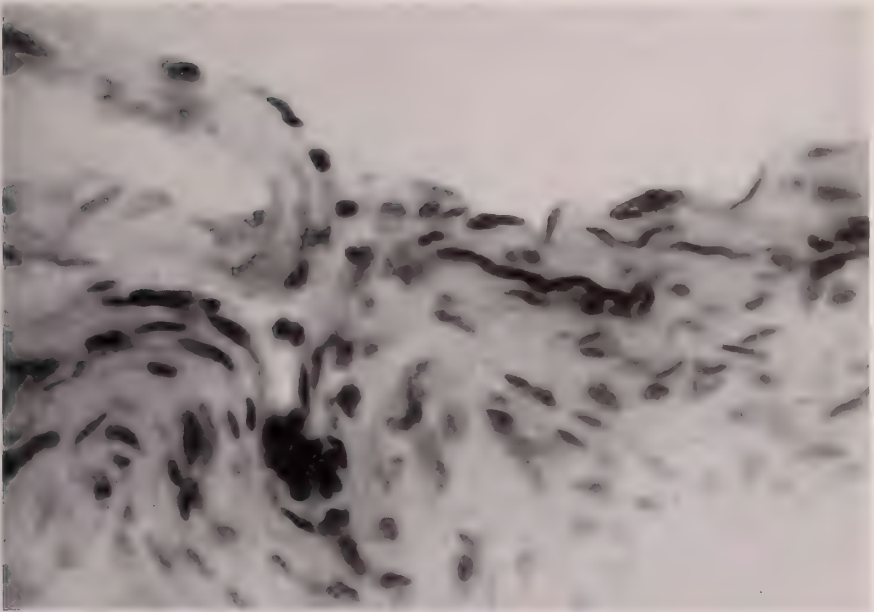


FIG. 14. *Trichinella* within the fibers of the leptomeninges (pia). Nissl.

There were no noteworthy findings in the kidneys, adrenals, urinary bladder, pancreas, thyroid, various lymph nodes, tonsils, or in numerous sections of the various voluntary muscles examined. Only in a few muscle fibers of the laryngeal muscle, particularly in those surrounding epiglottis and cricoid cartilage, some edema was noticed, with recent leukocytic infiltrations of the interstitial perimysial spaces.

The extensive preliminary search for parasites without any positive results remained, for a long time, most disturbing. It was only after repeated study of very numerous celloidin sections of the brain that part of a "stray" trichinella was found in the thalamus, fairly close to a disintegrating nerve cell (figure 13). We succeeded also in demonstrating, in additional sections, a few rare fragments of obviously dead parasites, strongly staining with hematoxylin, in the molecular zone of the cerebellum, and, by a rare chance, an apparently well preserved filiform young trichinella within the pia (figure 14) outside of a dense cellular meningeal infiltration of frontal gyri. Finally, serial sections of the laryngeal muscle disclosed, in an area not affected by any conspicuous change of myositis, a single well stained larva within or closely attached to the perimysium (figure 15) of a small fiber. Serial sections through the lumbar portion of the diaphragm remained entirely negative. Incidentally, however, marked inflammatory changes in the sympathetic ganglion of the solar plexus were observed, in the portion attached to the lumbar diaphragm.

The search for parasites in esophagus, stomach, small and large intestine, mesenteric lymph nodes, liver and spleen remained negative. Only in one lung section, in the interlobular space near the pleural surface, the head portion of a young trichinella was seen trapped between the edematous fibers.

DISCUSSION

We shall first reflect briefly on the history and symptoms of this case. The source of the infection could not be established. The boy, after recovery from whooping cough, was well for about one week and attended school. He died on the

ninth or tenth day, after the first symptoms of the trichinella infection were noticed. Whooping cough is not included among fifty different diseases or disease symptoms enumerated by Hall (1), which were misdiagnosed until their trichinous etiology became known. According to the family physician, this was a typical case of mild pertussis, for which, at the same time, another child in the neighborhood was treated. The cough had completely subsided for the last two weeks prior to the death of the child. The blood had not been examined. The only known blood count was taken two days before death and was typical of the rapidly progressing fatal cases. The absence or progressive drop of eosinophils in the blood is considered a grave symptom (11, 2). Rapidly fatal cases like ours have no eosinophils (12, 13, 14). Clinical laboratory observations on numerous German war prisoners, which had become simultaneously infected from the same source, revealed clearly an inversed relationship between blood eosinophilia and severity of symptoms (15).

As to the gross and microscopic findings in our case, they seem unique among the changes thus far reported in fatal trichinella infections of the central nervous system: the massive involvement of the cerebellum, particularly of one of its hemispheres, resulting in tumor-like swelling, with compression of the fourth ventricle and typical occlusion of the foramen magnum. Nor have we encountered any histologic changes comparable to the diffuse derangement of the architectural structure of entire cerebellar lobules. The complete disappearance and nearly complete destruction of numerous rows of Purkinje cells is the effect of ischemic necrosis, resulting in an unusually intense proliferation of glia cells throughout the molecular zone, more marked than in the well known reactions in typhoid fever and typhus (Spielmeyer). The causes for this actually laminary vanishing of the Purkinje cells are related to the intense inflammatory infiltrations of veins and capillaries in meninges, cerebellar cortex and white matter, to the swollen endothelial cells, the mass of the white blood cells and proliferating mesenchymal cells within the lumina and in the walls of the blood vessels, rather than to thrombosed blood. Such, at least, is the impression one gains from numerous celloidin sections in the most heavily damaged areas of the cerebellum. The vessels appear plugged by various nucleated cells, not by erythrocytes or fibrin.

That some parts of the central nervous system are obviously more affected than others explains the great variety of neurologic and mental disorders observed in patients with trichinella encephalitis. In the case of Bloch and Hassin (11), only the posterior half of the right hemisphere was found edematous; their patient had left hemiparesis and jacksonian seizures. Also, the focal type of cerebral injury was observed by Hurd (14) in 31 cases, one-third of whom died. In some cases of Sheldon's series (5), cerebellar signs, such as dizziness, ataxia and nystagmus, were the presenting symptoms. Vertical nystagmus at rest was the only abnormal neurological sign noticed in our case.

In the histopathological reports of fatal trichinella infections, no conspicuous involvement of the cerebellum has been thus far noticed. Hassin and Diamond found degenerative signs of the neurons very slight and no "strauchwerk". Outside

of the severe cerebellar changes and the distinct and diffuse meningitic process about brain and spinal cord, the inflammatory infiltrations in brain stem, basal ganglia and pallium are comparatively slight in our case, except for the lateral dorsal portion (cuneate nuclei) of the medulla and the medial areas of the thalamus, close to the ependyma. Thus, the entire histologic pattern of acute trichinella encephalitis in this case differs in location and character, with its profound meningitic and mesenchymal vascular reactions in the nervous parenchyma, from the various types of viral encephalitis and from the changes observed in typhoid fever and typhus. This, then, is contrary to the statements made in the original studies of the histopathology of trichinous encephalitis (7, 8). It appears to us that this severe inflammatory mesenchymal reaction, with the unusual abundance of eosinophilic leukocytes, should be regarded as suspicious if not actually specific for the fulminating type of trichinella encephalitis, even if the parasites are not detected by the usual routine examination.

The most consistent findings in trichinella encephalitis thus far reported are the granulomatous and glial nodules, especially in the white matter, formed around the parasites, the distinct perivascular mesenchymal inflammatory infiltrations and the marked edema, stressed particularly by Hassin and Diamond, Gamper and Gruber and by Globus. The difficulty in proving the presence of trichinae in the meninges is commented on by Davison (2), the rapid disintegration and fragmentation of the young larvae by Betzendahl (9). The more massive and intense the infestation of the central nervous system, the more pronounced is the mesenchymal reaction around the young larvae, which have escaped from the capillaries into meninges, subarachnoid space and brain substance. The intense eosinophilic reaction in our case, thus, is conditioned by this massive infection in connection with the disintegration of numerous trichinellae. Whether or not the known allergic constitution of the child, with the history of urticaria and hypersensitivity to insect bites, might have intensified the eosinophilic inflammatory response in the tissues of the central nervous system, we do not know. The extreme tissue damage in the cerebellum can be explained by selective infestation leading to severe ischemia. There appears to be no need to interpret this entire histologic picture as of a *more pronounced* allergic type.

As it took some time to prove, beyond any doubt, the parasitic cause, the data from the patient's history and the hospital record were carefully analyzed in an attempt to find out whether or not this severe encephalitic damage might have been a peculiar hypersensitivity reaction to penicillin. Such a speculation, however, could be discarded because symptoms of meningo-encephalitis had preceded, by nearly one week, the second intramuscular administration of penicillin. Also, the fatal cases reported as hypersensitivity reactions to penicillin (16, 17, 18), are of the classic anaphylactic or anaphylactoid type and the histologic picture in the central nervous system is characterized by recent multiple capillary hemorrhages and edema, but not by any type of a true inflammatory response.

As to the histologic findings outside of the central nervous system, we once more wish to stress the absence of changes of myositis. Only with the help of serial

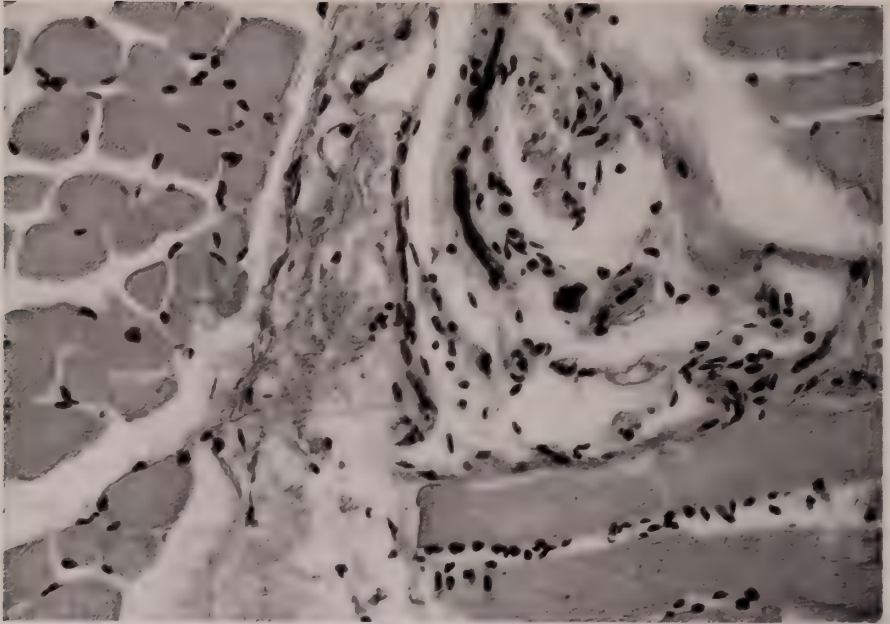


FIG. 15. Laryngeal muscle, edematous part. Dark staining young larva on the surface of a muscle fiber. Hem.Eos.

sections through an edematous portion of the laryngeal muscle, the single parasite, seen in figure 15, was detected. The recent inflammatory changes of the digestive system, particularly in the wall of the stomach and of the small intestine, point to the acute state of infestation. Here, particularly in the small intestine, the inflammatory exudate is exclusively neutrophilic and eosinophilic. The same interpretation can be given to the inflammatory response in the spleen and in the liver. The recent parietal thrombi in the right heart are probably of agonal type. It is of interest, however, that Sobel (13), reported a similar finding in a child which died from severe trichinella infection after an illness of only four days duration.

SUMMARY

In a sporadic trichinous infection, of a six year old boy, very marked, asymmetrical changes of cerebellar meningo-encephalitis develop, with extensive ischemic damage to several gyri and extreme inflammatory swelling, causing death by compression of the fourth ventricle. The cellular exudate in meninges and cerebellar cortex is predominantly eosinophilic. Histologic changes of myositis are almost completely absent, particularly throughout the diaphragm. Only prolonged search reveals a very few trichinellae in the meninges of the cerebellum, in the thalamus, in the perimysium of a laryngeal muscle fiber and in the edematous visceral pleura. This fulminating type of meningo-encephalitis, caused by trichinella infestation, appears histologically distinctive, if not specific: in regard

to the mesenchymal cellular components of the exudate, the intensity of vascular and glial reactions combined with effects of ischemia, and the paucity of cortical changes in the pallium. It differs also by the uniform meningeal involvement from the known types of viral encephalitis.

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STORAGE OF LIPOPROTEINS IN LIVER CELLS IN CASES OF CIRRHOSIS*

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In histological studies of various types of cirrhosis we have observed in the cytoplasm of the liver epithelium dense inclusions of a weakly basophilic substance which stained intensely with Gomori's aldehyde fuchsin (1) and with luxol fast blue.

A survey of the incidence of such inclusions in relation to various lesions of the human liver is presented and a preliminary attempt at their histochemical characterization described.

MATERIAL AND METHODS

Paraffin blocks of liver from 49 necropsies were used in this study. The material was fixed in Zenker's acetic acid solution; in only a few instances material fixed in 10 per cent formaldehyde was available. In two cases small pieces of liver which had been stored for nearly three years in formaldehyde were embedded in paraffin for special studies.

Sections eight microns in thickness were stained by the following methods: Ehrlich's hematoxylin and eosin, paraldehyde fuchsin (1) following treatment with Lugol's solution, Gomori's chrome alum hematoxylin, Weigert's resorcin fuchsin method for elastic fibers, Laidlaw's silver method, treatment for 30 minutes with Schiff's reagent, the periodic acid-Schiff procedure controlled by digestion for 30 minutes in saliva at 37° C., ninhydrin-Schiff method (2), Feulgen's method for DNA, methyl green-pyronine (3), ½ per cent aqueous toluidine blue directly or after the sections were subjected to treatment with acidified permanganate (4) or with concentrated sulfuric acid (5).

The following stains for lipids were employed in paraffin section, both, after fixation in Zenker's fluid and in formaldehyde; Sudan black in 70 per cent alcohol for seven minutes at room temperature, luxol fast blue counterstained with neutral red (6) or combined with the periodic acid-Schiff procedure (7).

The aldehyde fuchsin stain and Pearse's luxol fast blue method were also performed following treatment of the sections with various fat solvents for 18 hours at 37° C. (pyridine, equal parts of methanol and chloroform, acetone, di-ethyl-ether).

For comparison of the stored material found in liver epithelium with known

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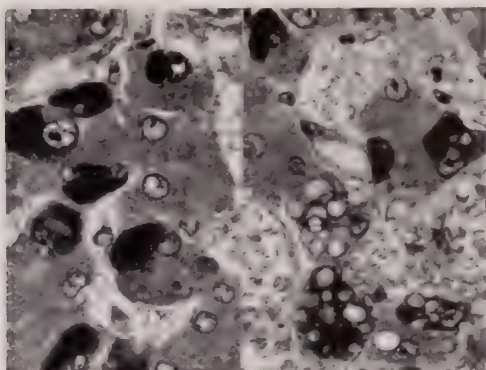


FIG. 1. Liver cells containing substance with affinity for paraldehyde fuchsin.

granular pigments the following methods were used: carbol fuchsin stain for ceroid (8); the ferric-ferricyanide test for reducing substances by Lillie's modification; peracetic acid-Schiff procedure (9).

RESULTS

a. In sections stained with aldehyde fuchsin some epithelial cells contained in varying quantity and distribution a substance varying from violet to purple in color which was always distinctly differentiated from the pale yellow cytoplasm of surrounding liver cells (Fig. 1). The intensity of the stain was uniform throughout in any particular case and the variations in shade were thought to be the result of fixation and later technical procedures. Deeper shades were obtained in material fixed in Zenker's or formalin when pre-treated with Lugol's solution. The affected cells were usually of the same size as their neighbors. The nuclei were well preserved and generally central in position.

The stained substance appeared mostly in compact slightly granular masses, either filling the entire cell or located in one part only. In such instances the substance appeared more or less sharply defined against the uninvolved portion of the cytoplasm. Occasionally, however, the substance was finely foamy but without clearly defined vacuoles. In other instances, especially in areas showing fatty change of the liver, numerous unstained vacuoles of varying sizes were included. Here, the borders of the stained inclusions were crenated and the vacuoles appeared like clusters of bubbles.

Where the stored substance filled only part of the cell it assumed a round or elongated shape. Sometimes it surrounded the nucleus in the form of a crescent or was located peripherally close to the side of the neighboring sinusoid.

b. *Incidence and intrahepatic distribution of the stored substance.* The findings described above occurred seven times in a series of 49 cases. Of the seven positive instances, four were found among nine cases of portal cirrhosis, two among three cases of post-hepatic cirrhosis, and one among five cases of chronic cholangitis.

The remainder of the series, included nine cases of other hepatic lesions in adults (cardiac cirrhosis, schistosomiasis, and one of hepato-lenticular degenera-

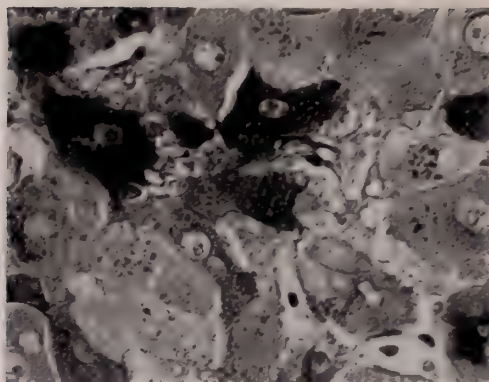


FIG. 2. The same substance as in the preceding figure, heavily stained with luxol fast blue-neutral red. The dispersed granules seen in other liver cells took a different brownish stain.

tion), five cases of severe hepatic lesions in infants, and 18 individuals dying of accidents or various diseases not affecting the liver.

The stored substance was only in one case evenly distributed throughout the liver, and under high-dry magnification every microscopic field included several affected cells.

In cases of cirrhosis some of the pseudolobules were involved, while others were free. If the pseudolobules were small, the affected cells were evenly distributed; but in large ones, the stored substance was more likely to be found in the vicinity of the fibrous septa than in the central portions.

c. Further staining characteristics. The stored material demonstrated with aldehyde fuchsin appeared morphologically identical but paler with Weigert's elastica method; it stained a gray to bluish-gray with Gomori's chrome alum hematoxylin.

Sudan black and luxol fast blue-neutral red gave intense staining of the affected cells. The luxol blue-neutral red method gave clear results only in formalin-fixed material no matter whether the material was embedded immediately after autopsy or after prolonged storage (Fig. 2); in material fixed in Zenker's, the neutral red stained the background too intensely. Treatment with fat solvents before staining with aldehyde fuchsin or with luxol fast blue neither decreased the intensity of the stains nor changed the foamy appearance.

Only after prior oxidation with acidified permanganate or after sulfation did the stored material stain orthochromatically with toluidine blue. Following sulfation, by contrast the reticulum and collagen fibers of the septa of the cirrhosis stained metachromatically (Fig. 3).

No elements were stained with Schiff's reagent alone. The periodic acid-Schiff procedure following digestion with saliva revealed only a few scattered purple granules within the epithelial cells, but throughout the liver cords many granules of yellowish pigment remained unstained. In one case part of this pigment was identified as hemosiderin with the Prussian blue test.

In sections where the periodic acid-Schiff method was applied after previous

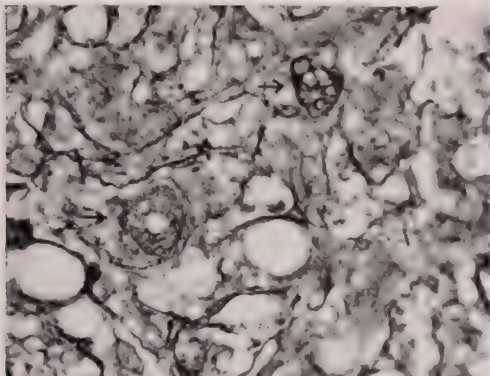


FIG. 3. Orthochromatic staining of the substance in liver cells. The reticulum fibers showed marked metachromasia. Toluidine blue following sulfation.

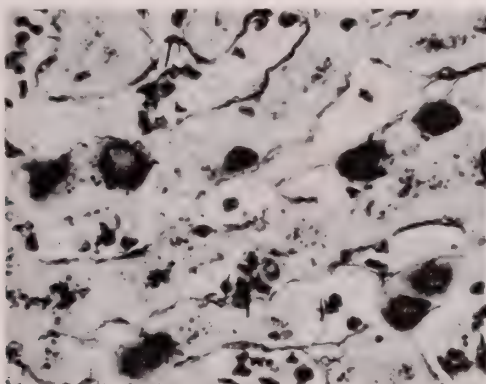


FIG. 4. Argyrophilic granules in liver cells containing stored substance. Laidlaw's reticulum method.

staining with luxol fast blue, purple granules appeared in similar concentration both within the lipid material and outside it.

The affected liver cells contained argyrophilic granules in varying quantity with Laidlaw's method (Fig. 4). The ferric-ferricyanide test and the peracetic acid-Schiff test were entirely negative. No acid-fastness was demonstrated except in a few scattered granules. The stored substance was negative with Feulgen's method and with methyl green. When stained with methyl green-pyronine mixture, intensely red staining foamy material was found in the affected cells.

DISCUSSION

The stored substance described in this paper is distinctive in that it is located only in the epithelium of the liver and not in the mesenchymal portion. Furthermore it is characteristic in appearance, occurring in homogeneous or foamy masses rarely containing clear vacuoles.

The fact that only paraffin blocks from our files were available for this study limited a histochemical investigation to the evaluation of certain tinctorial

qualities. The main characteristics of the stored substance were its affinity for sudan black and luxol fast blue, intense staining with aldehyde fuchsin, orthochromatic but never metachromatic staining with toluidine blue following oxidation with acidified permanganate or sulfation and, lastly, reduction of silver in alkaline solution.

The staining of paraffin sections with sudan black and luxol fast blue revealed the presence of lipids and presumably of phospholipids. This was confirmed by the dark blue-black staining of the substance with the modified luxol blue technic described by Pearse (6) who demonstrated that, if used as counterstain, neutral red enters a compound with luxol blue-phospholipid complexes. Extraction of the sections with fat solvents did not remove the lipid-like substance nor change its tinctorial characteristics. It therefore appears likely that a phospholipid is present presumably conjugated with proteins. This possibility is further supported by the result of the ninhydrin-Schiff procedure and the demonstration of pyroninophilia, suggesting, respectively, the presence of terminal amino acids and ribose-nucleic acid in the compound.

The failure of the lipid-containing substance to stain with Schiff's reagent directly or following oxidation with periodic acid makes it unlikely that carbohydrates are present in significant amounts. Likewise, the absence of metachromasia with toluidine blue even after the drastic treatment with sulfuric acid may, in the opinion of some authors, exclude the presence of carbohydrates (5).

The affinity of tissue structures for aldehyde fuchsin, although frequently found in matter reacting with the periodic acid-Schiff procedure, is also known to occur independent of the presence of aldehydes and mucopolysaccharides (4, 10). On the other hand, affinity of aldehyde fuchsin for certain special proteins has frequently been observed, beginning with Gomori's finding (1) that aldehyde fuchsin is taken up by the same cells in the anterior pituitary which are stained with chromalum hematoxylin and resorcin fuchsin. This parallelism has recently been demonstrated in secretions containing polypeptides and proteins (11) and was also observed in our material.

We have been unable to find in the literature any references to inclusions in the liver cells of adults presenting the morphologic and staining characteristics reported in this paper. Lillie (9) observed that "ceroid" may occasionally appear in liver epithelium in foamy masses. The substance described by us, like ceroid, stained with sudan black following embedding in paraffin, and showed argyrophilia. However, the failure to stain with Schiff's reagent following pre-treatment both with periodic acid and peracetic acid (9), the absence of acid-fastness, staining with chromalum hematoxylin and with luxol fast blue (3, 6), are not compatible with the definition of "ceroid" in the widest sense.

The only report of a protoplasmatic substance similar to that as found in our cases is that of Feyrter (12) who demonstrated "chromotrope Koernelung" in frozen sections of livers with the aid of his "Einschlussfaerbung" with thionine. These metachromatic granules which appeared in dense accumulations within groups of liver cells also stained black with the Smith-Dietrich method and were

negative with the periodic acid-Schiff technic. They were reported to be soluble in unspecified "fat solvents". Feyrter suggested that the granules represent accumulation of phospholipids. However, a comparison with our findings cannot be made at present in view of the different technics involved.

SUMMARY

Massive amounts of a hitherto undescribed substance were found in the hepatic epithelium in a number of cases of cirrhosis of different types.

The staining characteristics of the substance suggest that it is a lipo-protein complex.

ACKNOWLEDGEMENT

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ENZYMATIC STAINING REACTIONS IN REGENERATING TUBULAR CELLS OF THE RAT KIDNEY*

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A multitude of enzymes can be localized in various tubular segments in tissue sections of the normal mammalian kidney (1). In necrobiotic cells these staining reactions become weaker or disappear completely. However, the sensitivity of various enzymes to injury differs considerably. In general, changes take place more rapidly in cell damage induced by nephrotoxic drugs than in necrosis induced by ischemia (2).

In the present study, a number of enzymatic staining reactions were applied to kidneys in which regeneration had proceeded for various time intervals following the administration of a nephrotoxic drug. It had already been observed previously that in the regenerating cells of the proximal convoluted tubules, succinic dehydrogenase reappeared at an earlier date than alkaline phosphatase (3).

MATERIAL AND METHOD

Male albino rats of the Wistar strain were used. Toxic necrosis was induced by either DL-serine or mercury. DL-serine was given in amounts of one mg. per gram of body weight (4). The substance was dissolved in a few cubic centimeters of distilled water and injected intraperitoneally. Mercury (0.2 mgm. of mercury per gram of body weight) was administered intramuscularly in the form of Meralluride Sodium (Mercuryhydrin Sodium, Lakeside Laboratories, Inc., Milwaukee, Wisconsin). Animals were sacrificed after three, five, seven, ten, twelve, fourteen, twenty and twenty-eight days.

Tissues were fixed in 10 per cent formalin and stained routinely with hematoxylin eosin. The various enzymatic staining reactions were done on frozen sections that were cut as uniformly as possible at 10–15 μ thickness on a Sartorius freezing microtome. Sections were cut from fresh tissues or from thin tissue blocks that had been fixed for 18–24 hours in cold six per cent formalin neutralized with sodium hydroxide. The following staining techniques were applied to free floating sections

Succinic Dehydrogenase. The technique of Seligman and Rutenburg (5) was used on fresh frozen sections with the addition of several activators to the incubation mixture (3). The indicator substance was neotetrazolium chloride. Incubation time was 30–120 minutes.

Diphosphopyridine Nucleotide (DPN) Diaphorase. The technique used was that described by Farber and co-workers (6). A consistent staining pattern for

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(DPN) diaphorase is obtained if the incubation mixture contains the necessary substrates and co-enzymes. Neotetrazolium chloride served as indicator. Sections were incubated from 30–120 minutes.

Esterase. The azo-dye method using alpha-naphthyl-acetate (7) was employed for visualization of esterase activity in fresh frozen sections.

Glucuronidase. The method was that of Seligman and his co-workers utilizing 6-Bromo-2-Naphthyl- β -D-Glucosonide as substrate (8). As in the case of esterase, fresh frozen sections were used since fixation in cold neutral formalin leads to considerable inactivation of enzymatic activity.

Non-specific Alkaline Phosphatase. Frozen sections from fresh and neutral formalin-fixed tissues were stained according to Gomori's calcium phosphate technique (7), using ammonium sulfide for the demonstration of the formed cobalt phosphate precipitate. Incubation time varied from 5 to 30 minutes.

Non-specific Acid Phosphatase. In fixed and unfixed frozen sections Gomori's lead phosphate technique was employed (7). Incubation time was 10 to 60 minutes.

Non-specific Glycerophosphatase at pH 7.2. The technique used has been described previously and is essentially a modification of Gomori's technique for non-specific acid phosphatase (1). Incubation periods for fixed and unfixed sections varied from 30 to 120 minutes.

5-Nucleotidase. This technique is also based on a modification of Gomori's lead phosphatase technique using a pH of 7.2. Fresh and formalin fixed sections were incubated from 5 to 60 minutes (9).

Adenosine Triphosphatase. The incubation mixture in this technique is identical with that for 5-nucleotidase with the exception that the muscle adenylic acid is replaced by an equivalent amount of adenosine triphosphate (Sigma Chemical Company, St. Louis, Missouri). Fresh and formalin fixed sections were incubated from 5 to 30 minutes. (9).

Glucose-6-phosphatase. A modification of the original procedure of Chiquoine (10) was used on fresh frozen sections incubated for 10 to 15 minutes (11).

RESULTS

Following the administration of dl-serine, frank necrosis becomes manifest after three hours. The injury is limited to the terminal portions of the proximal convoluted tubules (4). In contrast, mercurhydrin in the large dose given damages not only the distal portions of the proximal convoluted tubules as seen with small doses, but necrosis often extends into the remaining segments of the proximal convolutions. Tubular regeneration becomes manifest after 48 hours. The necrotic epithelium is sloughed off and carried into the more distal segments. Remnants of necrotic epithelium were seen, however, even after two weeks. The denuded walls of the tubules were invested by proliferating cells which showed prominent nuclei and occasional mitotic figures. The cytoplasm of the regenerating epithelium was scanty and the height of the cells markedly reduced (Fig. 1). Even after 28 days regeneration was incomplete in many tubules. In these tubules the epithelium had not regained its normal appearance. It was flat and lacked

the eosinophilic staining properties which are characteristic for the normal proximal tubular cells. Following the administration of serine, moderate interstitial inflammation and connective tissue proliferation was noted. This inflammatory reaction was much more marked, and in addition, considerable calcification was seen in some of the necrotic tubules after the administration of mercury.

Histochemical Staining Reactions

A. *The normal rat kidney:* The enzymatic staining patterns observed in the normal rat kidney have been tabulated previously (1). Succinic dehydrogenase is most active in the proximal portions of the proximal convoluted and distal tubules and in ascending limbs of Henle's loops. Diphosphopyridine nucleotide

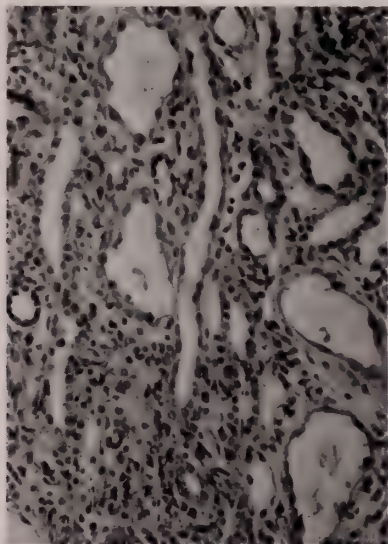


FIG. 1. Microscopic section of the kidney from a rat sacrificed 11 days after administration of mercurhydrin (0.2 mgm. of mercury per gram of body weight). An area of actively regenerating tubules is shown. Hematoxylin eosin $\times 250$.

(DPN) diaphorase is found in all tubular elements including the thin limbs of Henle's loops as well as in glomeruli and capillaries and walls of arteries.

Esterase and glucuronidase in unfixed frozen sections showed activity not only in proximal and distal convoluted tubules, but also in ascending limbs of Henle's loops and in collecting tubules.

In preparations stained for non-specific alkaline phosphatase and for non-specific phosphatase at pH 7.2, certain differences were noticed in fixed and unfixed sections. The deposition of cobalt sulfide and lead sulphide respectively was diffuse in the tubular cytoplasm in fresh frozen sections, but concentrated in the brush borders in fixed sections. Moreover, in the case of non-specific glycerophosphatase at pH 7.2, small spherical bodies could be made out in the cytoplasm of the proximal convoluted tubules in fixed sections. In such preparations, activity in tubules located in the medulla is repressed. Non-specific acid

phosphatase is found in all tubular elements. Enzymatic activity is localized within the cytoplasm and nuclei in the proximal convolutions, while the remaining tubules and glomeruli show mainly a nuclear reaction in both fixed and unfixed sections.

5-Nucleotidase is found in the proximal convoluted tubules and in capillaries located in the two outer thirds of the cortex, but not in glomeruli. In fixed sections activity is concentrated in the brush borders. Capillary staining is somewhat suppressed in such sections.

In sections stained for adenosine triphosphatase, there is striking activity in glomeruli, capillaries of medulla and cortex and in walls of arteries and veins. A positive staining reaction which is best visualized in formalin fixed sections is also observed in some tubular elements. It is strongest in ascending limbs of Henle's

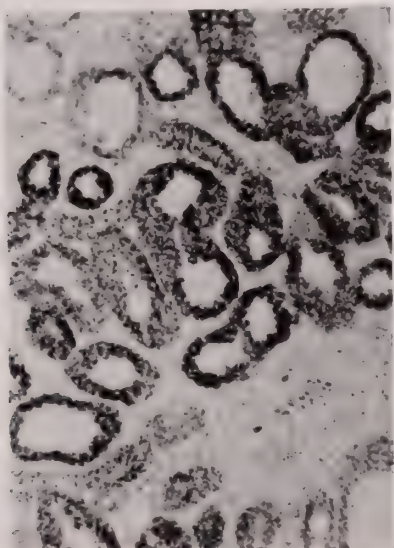


FIG. 2. A frozen section from the same kidney as shown in figure 1. Stained for (DPN) diaphorase. There is considerable staining in the regenerating tubules. $\times 250$.

loops and in distal convoluted tubules. In the proximal convoluted tubules it is seen in the brush borders. Finally glucose-6-phosphatase is detected mainly in the proximal portions of the proximal convoluted tubules.

B. Regenerating Tubules. Succinic dehydrogenase and (DPN)-diaphorase behaved alike. No unequivocal evidence of enzymatic activity was seen up to the fifth day; after the fifth day the cytoplasm contained occasional dust-like granules of reduced formazan. In the following days enzymatic activity was seen to increase in the regenerating tubules (Fig. 2). Even after 28 days, however, some tubules showed only little activity.

The staining patterns for esterase and glucuronidase were quite similar. Evaluation of the preparations stained with both methods was sometimes difficult due to some diffusion of the formed azo-dyes that indicate the site of enzymatic activity. Staining did not occur in regenerating cells before at least seven days had

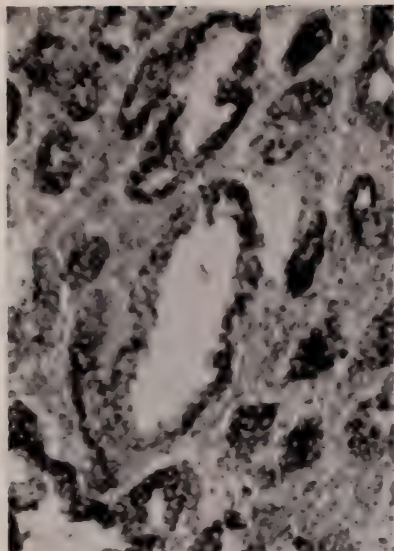


FIG. 3

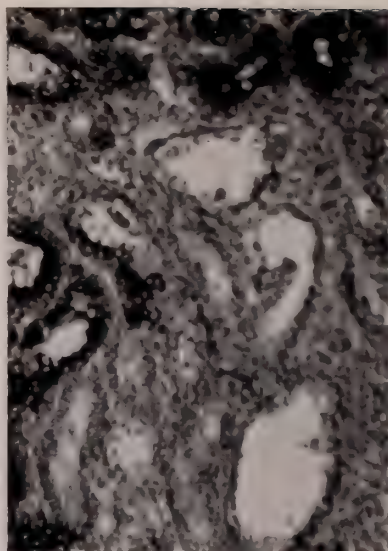


FIG. 4

FIG. 3. Unfixed frozen section from the same kidney as shown in figures 1 and 2. Stained for glycerophosphatase activity at pH 7.2. There is considerable activity in regenerating tubules. $\times 250$.

FIG. 4. A formalin fixed frozen section from the same rat kidney as shown in the other figures. Stained for alkaline phosphatase activity. There is no appreciable staining seen in regenerating tubules. Several undamaged tubules on the left upper border show a normal staining pattern. $\times 250$.

elapsed. Later, however, increasing numbers of regenerating tubules showed a positive staining reaction.

For the study of glucose-6-phosphatase, only the kidneys damaged by mercury could be used since the terminal portions of the convoluted tubules affected by dl-serine showed normally only a very faint reaction. Appreciable activity in regenerating tubules was found only in preparations after 11 to 14 days. Similarly, the appearance of adenosine triphosphatase and 5-nucleotidase was noted after 11 to 14 days.

Glycerophosphatase at pH 7.2 and acid phosphatase could not be detected in regenerating tubules in formalin fixed sections even after 28 days. In unfixed frozen sections, however, enzymatic activity became evident after 11 to 14 days (Fig. 3).

In the case of alkaline phosphatase in both fixed and unfixed frozen sections only traces of staining could be recognized in some of the regenerating tubules after 14 to 28 days (Fig. 4).

COMMENT

The results obtained in this study confirm and extend previous findings (3). They clearly demonstrate that regeneration, which commences within 48 hours after the cells have become necrotic, proceeds without any evidence of histochemically demonstrable enzymatic activity. This, however, does not exclude the possibility that small amounts of these enzymes are present in the early phase of

regeneration which cannot be recognized by staining techniques. The oxidative enzymes, succinic dehydrogenase and (DPN) diaphorase, reappear earlier than do the various hydrolytic enzymes that were examined in this investigation.

Dehydrogenase and (DPN) diaphorase are abundant in the normal proximal convoluted tubules not only of the rat, but in all mammalian species so far examined (1). Their slow reappearance in regenerating cells obviously indicates that the process of regeneration is not connected with the presence of these enzymes while the function of the tubular cells obviously is. The specific significance of most of the histochemically demonstrable enzymes is, however, not known with the possible exception of glucose-6-phosphatase. This enzyme probably plays a great role in intermediary carbohydrate metabolism. It reappears in the regenerating tubules relatively late. All the other enzymatic staining reactions reappear likewise only slowly in the regenerating tubules, glucuronidase and esterase somewhat earlier than the various phosphatases. It is of interest to note that only the faintest trace of alkaline phosphatase can be demonstrated within 28 days after regeneration has commenced, whereas phosphatase tested at pH 7.2 is noticeable within ten days. There is reason to believe that the optimal pH of phosphatase activity at substrate concentration that prevails in living cells is close to 7.2 (12).

Acid phosphatase and phosphatase at pH 7.2 are demonstrable in regenerating cells in unfixed frozen sections, but not in formalin fixed sections. This would indicate that under certain circumstances fresh frozen sections may give more information than fixed sections. This finding is the more interesting as the diffusion of enzymes into the surrounding medium is more marked in fresh than in formalin fixed sections (13).

The marked diminution of various enzymatic activities in regenerating cells so clearly demonstrated in these experiments is well correlated with the impairment of renal function which is observed following an attack of anoxic anuria, as it may follow an incompatible blood transfusion or an episode of shock (14).

SUMMARY

Enzymatic staining reactions for the demonstration of succinic dehydrogenase (DPN) diaphorase, esterase, glucuronidase, non-specific alkaline and acid phosphatase, phosphatase at pH 7.2, glucose-6-phosphatase, 5-nucleotidase and adenosine triphosphatase were applied to the rat kidney in which regeneration took place in the cells of the proximal convoluted tubules following the nephrotoxic action of dl-serine or mercury. Regeneration commences before any of the histochemically demonstrable enzymes reappear. Succinic dehydrogenase and (DPN) diaphorase can be visualized after five days followed by esterase and glucuronidase. The various phosphatases can be recognized a few days later, although alkaline phosphatase could be found only in traces even after 28 days. Regeneration, therefore, apparently takes place independently of histochemically demonstrable enzymatic activity. It appears reasonable to connect the impairment of renal function which is so prominent in the recovery phase of anoxic nephrosis with the deficiency of enzymatic activity in the renal tubules.

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HISTOCHEMICAL STUDIES OF FIBRINOID SUBSTANCES AND OTHER ABNORMAL TISSUE PROTEINS

III. PROTEOLYSIS OF FIBRINOIDS

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Following the demonstration by Klemperer (1) and his associates (2) that the vascular and connective tissue fibrinoid of systemic lupus erythematosus appeared to be related to protein of nuclear origin, the characterization of other fibrinoids became necessary. Klemperer indicated that the elucidation of the fibrinoid in the various "collagen diseases" could be of pathogenetic significance. In 1953, Klemperer (3) suggested that the various fibrinoids might be distinguished by their susceptibility to proteolytic enzymes. Experiments were initiated in this direction in conjunction with Dr. Mildred Phillips and have been carried on since then in other laboratories. The purpose of this paper is to present the apparent effects of proteolytic enzymes on certain fibrinoid substances as studied by histochemical and microchemical techniques.

MATERIALS AND METHODS

Human fibrinogen*: Fraction I of human plasma, 10 mg. per ml., in barbital buffer, pH 7.4.

Thrombin†: Bovine thrombin, commercial, in barbital buffer.

Trypsin‡: Crystalline trypsin in phosphate buffer, pH 8.2. Concentrations of solutions ranged from 0.1 mg. per ml. to 20.0 mg. per ml.

Pepsin§: Purified pepsin in 0.1 N HCl, pH 2.0. Concentrations of solutions ranged from 0.1 mg. per ml. to 15.0 mg. per ml.

Modified Carnoy solution: 3 parts of absolute alcohol to 1 part of glacial acetic acid.

Albumin§: Human serum albumin (salt free) in phosphate buffer, pH 7.5.

Tissue was collected at autopsy from two cases of generalized scleroderma, four cases of disseminated lupus erythematosus, two cases of florid rheumatic carditis, and three cases of malignant hypertension. These tissues were obtained from The Mount Sinai Hospital of New York, Hahnemann Medical College, Philadelphia General Hospital, and Children's Hospital of Philadelphia. Except for the fatal

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* Furnished by courtesy of the Physical Chemistry Laboratories, Harvard University.

† Purchased as commercial product (Parke, Davis and Co.).

‡ Worthington Laboratories, Freehold, N. J.

§ Armour and Co., Chicago, Ill.

cases of rheumatic fever, representative sections of kidney were fixed in modified Carnoy solution for 4-6 hours or quick-frozen by placing on dry ice. The Carnoy fixed material was processed in the usual manner, and the paraffin blocks were cut in serial sections at 3-5 microns. In addition, four left auricular appendages surgically removed during the course of mitral valve surgery were selected and prepared in the same manner. All sections were mounted on glass slides without the use of binding or adhesive agents.

Human fibrinogen (Fraction I) was reconstituted in phosphate buffer pH 7.5 and converted to fibrin by the addition of thrombin. Standardized clots were prepared and then fixed, embedded and sectioned exactly as the tissues. Trypsin, recrystallized twice as a crystalline protein was prepared in phosphate buffer pH 8.2. Concentrations of solutions ranged from 0.1 mg. ml. to 20.0 mg. ml. Purified pepsin was dissolved in 0.1 N HCl, pH 2.0 at concentrations from 0.1-15.0 mg. ml. Activity of the enzyme preparations was determined by the Worthington Laboratories and the Department of Biochemistry, Hahnemann Medical College. All experiments utilized buffer and inactivated enzyme as controls. Enzymes were inactivated by prolonged heating at 60°C. All active enzyme preparations were made prior to use, and stored at 4°C.

Prior to the experiments, all tissues were studied by Hand E, toluidine blue, aniline blue-chromatopre 2R, Alcian blue 8GS, PAS, PTAH and Wilder methods. The renal sections in scleroderma showed a fibrinoid "swelling" of the smaller arteries while in the lupus sections typical "wire-looping" was present. Severe arteriolar fibrinoid smudging was noted in the malignant hypertension sections. The fatal cases of rheumatic fever revealed fibrinoid alteration of the mitral valve and or in the connective tissue of the heart. In the auricular appendage sections, fibrinoid was demonstrated in the subendocardium in and about Aschoff bodies. The fibrin sections and albumin smears were stained in the same manner.

Human serum albumin was prepared as a 1% aqueous solution, and also stored in the cold. Smears of 0.05 ml. albumin on glass slides were allowed to dry and used as such or when necessary fixed rapidly. Regular bacteriological Petri dishes were used for incubation of the tissue sections. Two glass slides could be placed side by side on the bottom of the dish. The addition of 20.0 ml. of solution more than adequately covered the slide surfaces, and at any point reached an equivalent depth of 0.1 ml. With the top in place, it was easy to observe the sections without disturbance and note the effects of the various solutions on the tissues. On occasion, the tissue sections would float free in the media not containing enzyme and such experiments were discarded.

The tissue and fibrin sections were rapidly brought to water while the albumin smears were used directly. Table 1 indicates a typical experiment. Dishes I, II, III and IV represent the buffer, non-specific protein, inactivated enzyme and active enzyme controls. Only in dish V was the active enzyme preparation in contact with the tissue. The trypsin experiments were incubated for 8 hours while the pepsin series were incubated for 4 hours. Incubation was carried out in a standard 37°C incubator. At the end of the incubation time, the dishes were

TABLE I
Proteolysis under controlled conditions

Petri Dish Slides	I Tissue- fibrin	II Tissue-fibrin	III Tissue-fibrin	IV Albumin- fibrin	V Tissue- fibrin
Volume.....	20 ml.	20 ml.	20 ml.	20 ml.	20 ml.
Solution.....	buffer	1% albumin	inact. enzyme	enzyme	enzyme
Incubation.....	37°C.	37°C.	37°C.	37°C.	37°C.

decanted and the recovered solutions were filtered in the cold. Following filtration the solutions were stored at 4°C. All slides were immediately processed through the aniline blue—chromotrope 2R and toluidine blue procedures. Experiments were repeated utilizing different concentrations of enzyme. A total of 32 experiments represents the basis for this report.

Figure I shows the microscopic system used in this study. The photocell could be attached to the Leitz focaslide which in turn was connected to the microscope eyepiece by a bellows. At the top of the bellows, a ring adapter consisting of an iris diaphragm was inserted. By viewing the image through the focaslide periscope, the diaphragm aperture could be reduced in size to 5 microns and a single cell could fill the entire field. A standard Leitz 35 mm. camera utilizing Anscochrome tungsten or Ektochrome film was used to photograph areas under study. The detailed features of this optical system and its versatility will be presented elsewhere.

An ultraviolet spectrophotometric micromethod (4) for studying protein hydrolysis was used in an effort to determine the relationship between fibrinoid removal and protein digestion. A Beckman quartz spectrophotometer, model DU, with 10 mm. quartz cuvettes was used. Decanted solutions from dishes I, II, III and IV were utilized directly. However, in these studies, the experiment (dish V) was modified to exclude the fibrin slide since fibrinolysis would interfere in the determinations. Buffer solution was a 6% salt-sodium borate preparation pH 9.1–9.2. Quantitative estimation of amino acids was based on measurement of the ultraviolet absorption of their copper salts at 230 μ . Samples were obtained at 1, 2, 4, 6 and 8 hours after incubation.

RESULTS

Fibrinoid was present in the walls of the renal vessel in the cases of scleroderma, systemic lupus and malignant hypertension. Some of their histochemical properties are listed in Table II. The susceptibility of the various fibrinoids to enzymatic digestion is illustrated in Figure 2. The fibrinoid of malignant hypertension was most sensitive to trypsin activity while the fibrinoid of scleroderma was extremely resistant. Removal of fibrinoid was first estimated by measurement of light transmission after staining when compared to the stained control specimens. However, due to the selective sampling, the data obtained was of doubtful quantitative significance. Visual interpretation of the tissues proved to be just as useful for qualitative estimation of fibrinoid digestion. Thus, Figure 2

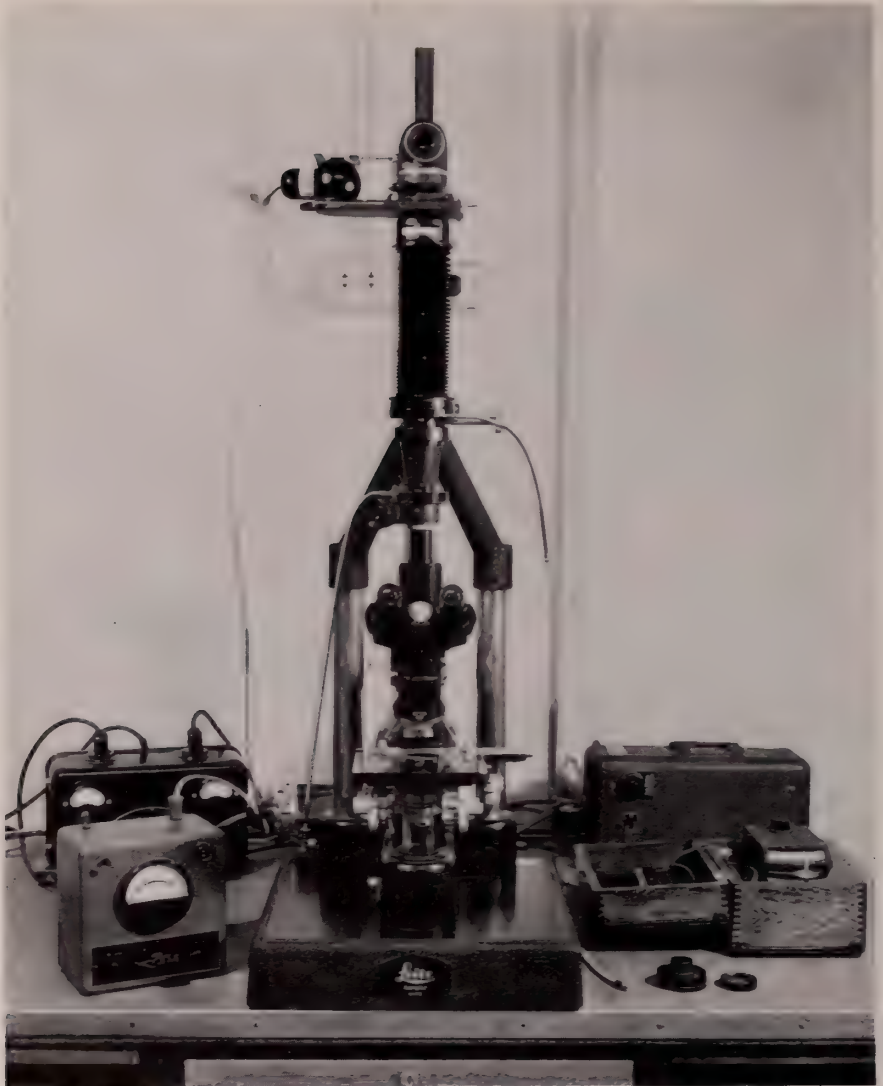


FIG. 1. Leitz UAM microscope with accessories for light transmission measurements of single cells or restricted areas up to 5 microns.

should be regarded as an approximation of the gross tissue changes and represents an average of three experiments. It can be seen that the fibrinoid of rheumatic carditis and systemic lupus occupy intermediate positions. The experimental results obtained with varying concentrations of pepsin were not clear, and are not included in this presentation.

The purpose of the albumin solution was to control the possibility of non-specific adsorption of protein. Such adsorption might block reactive staining sites thus imparting a false impression of fibrinoid "digestion". For the same reason, inactivated enzyme was used as a control. Trypsin and pepsin routinely removed albumin and fibrin from the slides as evidence of enzyme activity.

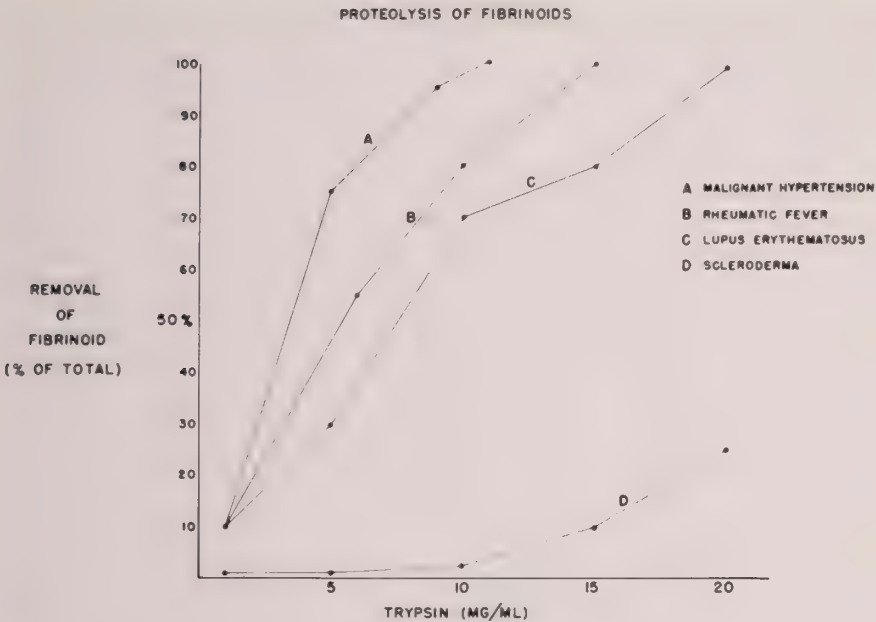


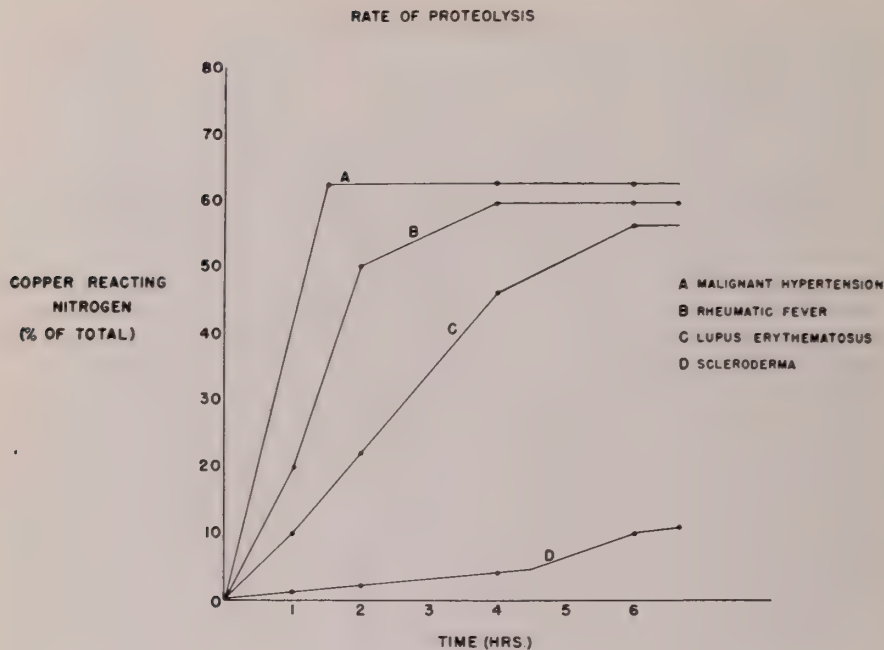
FIG. 2.

Attempts to relate the visual observations of fibrinoid removal with proteolysis were attempted according to the method of Spies (4). Figure 3 demonstrates the results obtained by this method after a limited number of experiments. Only one out of every three experiments yielded satisfactory results. The reasons for this are not entirely clear and possible explanations are being explored. Nevertheless,

TABLE II
Properties of various fibrinoids

	Scleroderma	S.L.E.	Rheumatic Carditis	Malig. Hyper.
H and E.....	Red	Blue-Red	Red	Red
Aniline Blue.....	Varied Shades	Bright Red	Bright Red	Bright Red
Chromotrope.....	of Red, Pink, Blue			
PAS.....	Pink	Pink-Red	Red	Red
Tol. Blue.....	Orthochro- matic	Variable	Metachro- matic	Orthochro- matic
Test. Hyaluronidase..	—	—	Complete Di- gestion	—
Ninhydrin-Schiff	Red	Red	Red	Red
SH, S-S.....	+ +	—	+ +	+ + +
Phospholipid.....	—	—	—	+ +
Potassium.....	—	—	+	+ + +
Cholesterol.....	—	—	—	+ +

Table II. Table demonstrates some of the properties of fibrinoid present in scleroderma, systemic lupus erythematosus (S.L.E.), rheumatic carditis, and malignant hypertension (Malig. Hyper.). No effect indicated by — and total digestion + + + +.



the method may allow for the separation of similar materials by differential spectrophotometry. Such a method has been developed for studying other enzyme systems (5).

DISCUSSION

The common denominator which served to link a variety of systemic connective tissue diseases into a distinct group was the presence of fibrinoid (16). Klemperer's original concept has served to focus attention on this material as a possible key to the pathogenesis of these maladies. By virtue of its location and quantity in tissues, the various fibrinoids are difficult to analyze. Methods of extraction and chemical analysis have been attempted by several workers (7, 8). A wide variety of histochemical, immunohistochemical and microchemical techniques have been applied in attempts to characterize the fibrinoid substances. The accumulated data when interpreted within the framework of the disease processes indicates that a variety of distinct fibrinoids exist.

The histochemical observations of the fibrinoids (9) strongly suggest major differences between the individual members of the "collagen disease" group and other conditions. Altshuler and Angevine (10) indicated that fibrinoid represented a precipitation of basic protein and acid mucopolysaccharide in the ground substance. The histochemical analysis of the fibrinoid in malignant hypertension suggests an origin from smooth muscle (11). The characteristic fibrinoid deposits in systemic lupus erythematosus contain a protein moiety of nuclear origin (2). Studies in rheumatic fever support the contention that an acid mucopolysaccharide probably of the chondroitin sulfate-like type is intimately involved in

the formation of fibrinoid (12). The fibrinoid of scleroderma appears to be closely related to a "soluble" form of collagen (8).

Recent studies by Vazquez and Dixon utilizing fluorescein labelled rabbit anti-human gamma globulin, have demonstrated the presence of gamma globulin in the fibrinoids of rheumatic fever, systemic lupus and rheumatoid arthritis (13). Mellors and his associates have made similar observations (14). However, whether the localized gamma globulin represents antibodies remains speculative. Gitlin, Craig and Janeway using an anti-fibrin fluor, have shown the presence of fibrin in the fibrinoid of all the collagen diseases they have studied (15). The repeated demonstration of gamma globulin and fibrin in several fibrinoids further emphasizes that these tissue substances are mixtures of important biological materials.

The separation of the fibrinoids presented in this study by their differential susceptibility to proteolysis favors the concept that they are a heterogeneous group. Because of the nature of the procedures used, the results are not of quantitative significance. Nevertheless, they sharply delineate these fibrinoids on a relative scale. By using serial sections and a battery of controls, the observation of preferential enzyme activity with apparently similar substrates strongly suggests differences in substrate composition. The exact nature of these differences and their evolution as morphological entities awaits further investigation. The preliminary data indicating an increase in products of protein hydrolysis in the enzyme containing media further confirms the presence of protein in fibrinoid. The rates of hydrolysis, Figure 3, again demonstrate physicochemical variations in the fibrinoids studied.

Previous inability to digest fibrinoids with fibrinolytic enzymes (16) in view of the findings of Gitlin, Craig and Janeway, does not negate their observations. As these workers state the detection of fibrin in tissues by the use of dye techniques is extremely variable. The reactive sites of fibrin deposited in tissue may be blocked preventing the action of a purely fibrinolytic enzyme. However, proteolytic enzymes are capable of digesting such material. The results obtained in the present study may be influenced by the age of the fibrinoid which depends on factors determining the temporal course of the disease. The homeostatic mechanisms regulating the steady-state of the ground substance and connective tissue appear to be intricately involved (17). The various fibrinoids seem to represent the tissue expression of altered connective tissue homeostasis. Investigation of all aberrations of connective tissue (18) may elucidate the exact interrelationships of the various constituents in fibrinoid.

The concept of the "collagen diseases" by Klemperer has inspired and stimulated research around the world in a much neglected area of human disease. Klemperer demonstrated in an outstanding manner that anatomical pathology continues to serve as the foundation for the analysis of disease. It is in this spirit and tradition that the present and related studies have been done.

SUMMARY

Fibrinoid of the renal vessels in fatal cases of generalized scleroderma, systemic lupus erythematosus and malignant hypertension was studied. Aschoff bodies demonstrating fibrinoid were evaluated in surgically removed left auricular

appendages and fatal cases of rheumatic carditis. Subjecting these fibrinoids to controlled trypsin digestion, a differential susceptibility to proteolysis was observed. Preliminary measurements seem to indicate that the proteolytic reaction rates also vary. These data confirm previous histochemical and immunochemical observations as to the protein composition of fibrinoid. The factors probably responsible for the physicochemical properties of these substances are discussed. The hypothesis that a variety of fibrinoids exist is substantiated.

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FACTORS IN THE CAUSATION OF LEUKEMIA*

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The epidemiology of leukemia has become of increasing interest as study is given to the relationship of the disease to industrial and other toxic products, viruses, genetic factors and ionizing radiation. A critical examination of leukemia as related to radiation is of special interest in view of the rapid expansion of use of atomic energy with the possibility of exposure of numbers of population to radioactive waste products. The prevalent use of radiation in medical diagnosis provides a further stimulus to consideration of its possible leukemogenic effect.

While the various manifestations of leukemia and lymphoma have much in common, there are enough differences between types of the disease group to indicate that they do not constitute a single disease process with a single cause.

Attention must be given to the hypothesis that more than one factor may be concerned in the production of the disease in any given instance, since there are many forms of cancer in which co-carcinogens are of importance (1).

The general prevalence of leukemia is difficult to determine with accuracy, and often large masses of vital statistics do not include adequate breakdown as to type. In the United States in 1953, there were 19,576 deaths from neoplasms of the hematopoietic and lymphatic systems, a rate of 12.5 per 100,000. Deaths from leukemia comprised 6.3 per 100,000 (2). In a study of incidence of leukemia among several million inhabitants of Brooklyn, New York, 6.44 fatal cases per 100,000 living population were found by MacMahon and Clark (3). For the United States population over 20 years of age in 1950, (thus omitting the acute leukemias of childhood), the mortality rate from leukemia was 3.9 per 100,000 population.

In Massachusetts there were 311 deaths from leukemia in 1950 (116 lymphatic type and 87 myeloid) and 337 deaths in 1955 (115 lymphatic and 108 myeloid).

Since leukemia is a fatal disease, its mortality rate is essentially its rate of incidence, and mortality figures may be used as a basis both for total incidence and for distribution of types of the neoplasm.

Leukemoid reactions offer difficulty in clinical diagnosis and may confuse efforts to determine the frequency of the disease in clinical studies. In general it may be assumed that in fatal cases adequate diagnosis has been made and that a diagnosis of leukemia recorded on the death certificate is fairly accurate.

For purposes of this study, we have classified leukemia as myeloid, lymphatic, monocytic or undetermined. The clinical classifications of acute or chronic, while useful, are difficult to apply, since chronic cases may sometimes terminate in acute form. However, acute leukemia is more frequent in the first two decades of life when the chronic forms are rare.

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TABLE I

Distribution of leukemia according to type in some recent surveys
 [Modified and Expanded from Gunz and Hough (4)]

Authors	No. of Yrs. Covered	No. of Cases	Per Cent of Total Cases			
			Myeloid	Lymphatic	Monocytic	Unclassified
Rosenthal, 1954	7	489	73.9	24.6	—	—
Gauld et al, 1953	14	647	36.9	54.2	8.8	—
Latourette et al, 1954	15	927	34.8	36.3	14.8	15.9
Best and Limarzi, 1952	26	916	38.7	37.5	4.3	18.6
Gunz and Hough, 1956 (4)	5	553	41.2	37.9	1.3	16.5
MacMahon and Clark, 1956 (3)	10	1709	50.5	36.3	4.9	8.1
Lange, Moloney and Yama- waki 1954 (5)	4	a) nonexposed	a) 55.0	a) 34.6	a) 8.1	a) 2.0
		Japanese 49				
		b) exposed	b) 68.0	b) 17.3	b) 4.0	b) 10.6
		Japanese 75				
Present autopsy series	36	183	42.6	40.4	4.4	12.6*

* Include 4.4% plasma type.

Data from 5,214 autopsies on cases of cancer done in a group of hospitals associated with this laboratory from 1920 to date have been tabulated. Among them are 183 cases of leukemia, 3.5 per cent. Of these, 40.4 per cent were lymphatic in type, 42.6 per cent myeloid, 4.4 per cent monocytic, 4.4 per cent plasma cell and 8.2 per cent undifferentiated.

Table I gives a general survey of recent data bearing on the distribution of different types of leukemia and indicates that the myeloid form is most common, though only slightly so. Classification as to chronicity has been disregarded.

As an example of leukemia associated with toxic agents the Massachusetts experience with benzol may be cited. Among 89 workers with benzol poisoning studied by Hunter, 2 died of leukemia, and several others showed blood dyscrasias (6, 7). Myeloid metaplasia, sometimes associated with benzol poisoning, may manifest leukemoid reactions or progress to true leukemia.

In recent years renewed emphasis has been placed on the possible viral origin of leukemia. Lymphomatosis (8) in fowl is thoroughly established as a viral disease. That leukemia may be of viral origin in mammals is less definite but strongly suggested (1, 9).

Genetic susceptibility to leukemia is well established in mice (10, 11). Most leukemias in mice are of lymphoid type and in some, at least, originate in the thymus. In man there is not clear evidence as to the importance of heredity but there is much evidence that leukemogenic stimuli are strongly modified by the genetic constitution of the host as well as by his hormonal balance and state of nutrition (12, 13). Experience both in man and in animals seems to indicate that leukemia is not primarily hereditary, although strains in which leukemia has a high incidence have been developed in laboratory animals.

Ionizing radiation has been associated with the causation of leukemia either as

a cocarcinogen (14) or as the chief inciting agent (15). The total doses of ionizing radiation which have preceded the appearance of leukemia in man are in the aggregate high. Thus, in most of the radiologists who have developed leukemia, there is evidence that much of the body had received an aggregate dose of several hundred r (16), although absorbed in small increments over a long period of time.

This relation to dose is shown among the survivors of the atomic bombing of Hiroshima. Those closest to the hypocenter and therefore probably receiving higher doses of radiation showed a sharp increase in incidence of leukemia as compared with those at a distance and over the control population. Within the 1000 meter distance over 1 per cent of survivors have thus far developed leukemia (17). When radiation is given to a portion of the bone marrow, as in the x-ray treated cases of ankylosing spondylitis studied by Court-Brown (18), there is a definite increase in the incidence of leukemia with increase in dose. Two cases developed following doses of less than 500 r to the spinal marrow. Court-Brown and Doll (19) found the dose response relationship to be linear when the relevant cases of leukemia were related to the man years at risk and when only spinal irradiation or maximum spinal marrow dose was considered. They further suggest that there may be no threshold dose for the induction of the disease.

It is not clear as to whether there is a definite threshold level of ionizing radiation for leukemogenesis, but for all practical purposes, it may be assumed that there is a threshold because the increase, if any, at low doses of radiation is so slight that it cannot be detected.

Leukemia associated with ionizing radiation has followed chiefly external radiation received either in single or divided doses. There are scattered cases where leukemia has followed the administration of therapeutic doses of radioactive iodine (20). While the dose level was possibly adequate to incite leukemia in several of the cases, it is probable, as Pochin (21) has pointed out in his case of acute lymphatic leukemia following administration of radioiodine, that the development of the disease was merely coincidental. Probably the total dose to the lymph nodes nearest to the thyroid was about 70 reps, while the liver might have received as much as 100 reps. The thyroid gland itself received a total beta-gamma dose of 6170 reps. As Pochin suggests, had there been lymphoid aggregates within it which served as a focal point for development of the leukemia, the distribution of lesions would have been quite different.

From data thus far available, it appears that ionizing radiation is a cause of leukemia in man. The dose required appears to be large, on the order of several hundred r. Either a single large dose or multiple small doses may be leukemogenic. Exposure of a major portion of the hematopoietic or lymphopoietic tissue appears necessary, although in rodents radiation of the thymic region alone may be followed by lymphatic leukemia. Even doses approaching the lethal range fail to produce leukemia in many persons. Hence, radiation is not the sole factor in production of the disease.

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THE JEW AS PHYSICIAN: HISTORICAL PERSPECTIVE OF HIS CONTRIBUTIONS TO MEDICINE

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In the annals of medical history much is to be found on the place of the Jew in medicine. A great deal, too, has been written on Jewish contributions to medicine. But startling as it may sound, the question may well be asked, are there Jewish contributions to medicine? It is true, of course, that Jews have made innumerable, some very great, medical contributions in the nineteenth and the twentieth centuries, but one may reasonably ask, what is there Jewish about them? Ehrlich was an inspired genius, he laid the foundations of modern immunology and chemotherapy, and he was a Jew. However his great discoveries are not any more Jewish than Pasteur's discoveries in bacteriology are French or Harvey's discovery of the circulation is English, or the discovery of anesthesia by Americans is American. The error lies in the confusion of two entirely different concepts, namely, contributions by Jews and Jewish contributions. The statement may be made with complete assurance that, with two very great exceptions presently to be considered, there is nothing Jewish about the contributions made by Jews. Quite simply, they were contributions to medicine. There is one additional less well defined contribution of considerable social-historical importance which will become evident in the course of the discussion.

Without making undue claims, it may be set down as a fact that the place of the Jew in medicine is an honorable one. During the early and intermediate middle ages, when Christian Europe was medically asleep and the flame of medicine was kept alive by the Arab world, it was fanned almost as vigorously by Jews. The so-called golden period of Arab medicine may with considerable truth also be called Judaeo-Arab. But it is not too heretical to say that the period was not very golden, since there was little originality and practically no science. The great debt we owe those scholars is for keeping alive and making accessible the works of Hippocrates, Galen and other classical writers, who would otherwise have continued to moulder and be forgotten, and for laying the foundation for the renaissance of medicine. It is worth stressing, however, that over-enthusiastic historians sometimes read into the observations of ancient and medieval writers knowledge which they did not possess and attribute to doctors of old scientific insight of which they were obviously bereft.

There is no mention of physicians in the Bible. None is recorded by name comparable to the great doctors in the Hippocratic age, none in the days of the Alexandrian school and no Jew of eminence in the subsequent centuries loosely known as a Graeco-Roman period. Indeed, after the great awakening which came with the birth of the Universities, in Salerno, Montpellier, Paris, Padua, Bologna, no Jewish names comparable to Lanfranc, Mondeville, de Chauliac and later Vesalius and Sylvius appear on the horizon, although there is on record a host of

Jewish physicians who practised the good medicine of the day, some of whom left written works of considerable historical merit. Whether or not those were great doctors is a matter of dispute, but that they were good practitioners, much sought after, is not to be doubted. This is amply attested by the fact that they were physicians to kings and princes, popes and cardinals, sultans and viziers, and were trusted as physicians despite being held in low esteem as Jews. But this, too, is worthy of note, though Jewish practitioners of medicine continued in an unbroken line, it was only after the advent of the nineteenth century, and first in virulently antisemitic Germany, that really great Jewish names begin to appear.

There are reasons for this. Despite Jewish emphasis on the worth and dignity of the individual even in very early times, practically all social activities were communal in nature and regulated by religious and social precepts. Like everything else which touched the individual and society health and disease, too, came from the Lord. The priests were the purveyors of what little medical knowledge existed at that time. Long before the Hebrews entered on the scene of history the Egyptians recorded by name practitioners of medicine and even "specialists". Not so the Jews. Here and there, and much later, there is mention of the practice of medicine by priests and prophets, generally in the performance of miracles. Elijah and Elisha resuscitated the dead and Isaiah cured King Hezekiah.

And yet out of this anonymity, derived from a profound social sense and rooted in communal needs, there appears a medical contribution of monumental importance. It is the well recognized principle of quarantine. Whence it came is not known. The Egyptians are silent on the subject. Perhaps it was borrowed from the Babylonians, but there is no evidence. For the first time in recorded history we hear of legislation to isolate the sick and to remove them from camp in order to protect the community. The Bible speaks of *Tsaraath*, which is erroneously translated as leprosy. Whatever the nature of the illness the sick person must stay away from his home a whole week, if need be two weeks. He is to perform ablutions to cleanse himself of disease lest he carry it back to camp. In severe cases the clothing is to be burned. The priests are the sanitarians. This sanitary code is the first known beacon to light the road of preventive medicine. It is the beginning of the concept of infection, even though there is no evidence of scientific knowledge of its meaning or of the significance of transmitting disease by contagion. The work quarantine is Italian and came into use two and a half thousand years after the introduction of the practice when the period of isolation was changed to forty days. We are dealing here with a novel concept embodying the first step in preventive medicine, legislated by a primitive people with little medical knowledge. It is a very great medical-social concept and a significant realistic approach to health and to social well-being.

The other peculiarly Jewish medical-social contribution is the introduction of the Sabbath. Most of the emphasis on the one day of rest in seven days has been put on its social and economic importance. Its great value to health and life has not been fully appreciated and yet this revolutionary introduction of a day of rest, of complete release from work, has become the greatest boon to health, a great release from fatiguing labor. It provided the necessary time for recuperation

and for husbanding one's strength. Again, whence it came is not definitely known. Perhaps Moses borrowed it from the Babylonians, but if so he changed its meaning, gave it new significance and transmuted evil into good. It is recorded in Marduk's tablets that "every seventh day was sacred to the moon god Sin, an evil day on which man dare not eat cooked flesh, change his garments, offer sacrifices, ride in a chariot, speak a malediction, or begin anything new lest the venture be attended by misfortune".* Whatever its source, the Sabbath now was made for man and became a beneficent day, a day of joyful rest, a health-giving respite. In this, too, is embodied the concept of communal health and of social ethics. A very great Jewish medical contribution indeed and evidence of realistic thinking. The idea of legislating a day of rest and of enforcing a health-giving measure among primitive tribes further reflects intense realistic concern with the welfare of the group. It bequeathed a boon to untold future generations. The concept became so deeply rooted in the ethics and mores of the Jew that he often forfeited his life as a captive in war or a slave among his enemies rather than desecrate the Sabbath. Contrariwise the Jew enjoined his own slaves to rest on the Sabbath.

As we come down the stream of history, even after Alexander the Great brought Greek culture into intimate contact with the Jews, there still is no Jewish medicine as we know it in the Hippocratic writings. Not even the proximity of Alexandria with its great medical schools created by Herophilus and Erasistratus gave impetus to medicine in Judea, despite the fact that there was a great Jewish community in the city at the mouth of the Nile. Only after the first century of the Christian era do we hear of a physician. Samuel Yarhinai is his name, but what kind of a doctor he was and what he did we are not told. We know that he was an astronomer, as his name implies, that he was a Talmudist, and that he was physician to *Ychudah Ha'nasi* author of the *Mishna*. Mention is made of the fact that judicial councils forbade the practice of medicine without a license, but here again we are not told what knowledge the license prescribed and who was to be licensed. The Talmud dealt with matters of health and sanitation, and discussed in the learned fashion of the day anatomy and hygiene, but all of it from the point of view of religion and all of it by scholars versed in the Law and not in medicine as a discipline. There is even mention of one Aba Saul, who appears to have been something of an embryologist; in point of fact, we are told that he was a gravedigger.

With the destruction of the temple by Titus in the year seventy and the further destruction of all Palestinian Jewry when the last great rebellion of Bar Kochba was put down sixty years later under Hadrian, the scene of Jewish life and learning begins to shift to Babylonia where academies thrive in Sura and Pumbeditha, although the Jerusalem Talmud is still being compiled in Palestine. Jews continue to live in large numbers in Alexandria, where Philo presides over philosophy, and all over the Roman empire from the Euxine to Gaul and Spain. We know that there are Jewish physicians, but there is none of eminence and none during the early centuries has survived by name. Christian persecution grew fiercer in

* Quoted from *Man and His Gods* by Homer W. Smith.

proportion as the Church grew stronger and more pervasive until Honorius in the early fifth century and Theodosius late in the same century forbade Jews to practise medicine. A thick curtain is drawn over Jews in medicine for the next two hundred years. Not until many years after the conquests of Mohammed with the spread of Islam and the consolidation of the Arab sway in the East do we begin to hear of individual Jewish physicians. When Harun al Rashid founded the Baghdad University we hear that Jews learned in medicine take active part.

As the Arab empire spreads to Egypt and westward into northern Africa, thence into Spain and Sicily, and its sway over the new dominions is firmly established, academies of learning arise and medicine, too, begins to flourish. Isaac Israeli is mentioned by name as a learned physician in Egypt. He was born in 850 and is said to have lived one hundred years. Cairo has its university and there is a medical school in Karaiwan in northern Africa, but the famous period of Judaeo-Arab learning begins in Moorish Spain. Salerno makes its appearance in Italy as the first of Universities. Sabbato ben Abraham Donnolo, born in 903 and still alive in 982, studied in Salerno and left to posterity the oldest Hebrew medical manuscript extant and the earliest Italian medical work. Montpellier has its medical school and so has the University of Paris. Individual Jews attend now and then. There is even mention of Jewish professors and, apocryphally perhaps, of a Jewish dean at Montpellier. In the main, Jews do not study medicine at Universities, and they do not flourish as teachers. The Christians do not want them, and Jews learn the art from books and by apprenticeship, as do most leeches of the day. Evidently they are trusted, since many Christians, especially soldiers of eminence, nobles and princes, and even high religious dignitaries, seek them out despite the repeated injunctions of the church which forbade the practice of Jewish doctors among the Christians. The reason given was that a Jewish doctor may impair the morals of Christians and make them stray from the faith. Many Jewish physicians suffered when treating non-Jews. A doctor Lopez of London, physician to good Queen Bess, lost his life after being falsely accused of trying to poison his sovereign. Marlowe wrote *The Jew of Malta*, a scurrilous drama built around an impossible Jewish ogre, just to inform the English what monsters the Jews were.

Being literate the Jewish doctors write books, which is really copying old masters, perhaps with a personal slant. They translate from the Arabic, especially into Hebrew. There are many translators, of whom the ibn Tibbons, themselves practising physicians, are the most illustrious, but there are others, too, many of the translations resting peacefully on dusty shelves and known only to antiquarian scholars who love musty archives. But there is a difference. The Jewish physician of those days was not only a leech practising good or bad medicine, as the case might be; he frequently was a Hebrew or Arabic scholar of parts. Very often he was a great rabbi. Maimonides is the most famous of them. He composed nine "books" on medicine, the while he wrote the *Mishne Torah* and the *Guide To The Perplexed*. Like other philosophers he sought, not too successfully, to reconcile religion and reason and tried to mix Moses with Aristotle. Less well known but also a very great rabbi and scholar and physician was Nach-

manides, who defended Jewry in some of its darkest hours of the middle ages. Perhaps the greatest of all Hebrew poets since the dispersion, Jehudah Halevi, was a doctor of medicine, though how good we do not know. Another famous rabbi and commentator and poet and physician was Abraham Ibn Ezra. Ibn Gabirol, for long known to Christian scholastics as the philosopher Avicbron until rescued by Jewish scholars, regarded as a poet of only slightly lesser stature than Halevi, also practised medicine. Curiously, the church father Jerome reproached Jewish scholars for wasting their time in the laboratories of physicians.

Besides being physician-poets, physician-scholars and physician-rabbis many were also communal leaders who represented their people in good and evil days and often were compelled at the risk of life to defend their bretheren when reviled or persecuted and to rescue them from threats of extermination by an appeal to princes and kings and cardinals and popes. There is an illustrious roster of physician-statesmen who served their kings and lords and high ecclesiastics. Many were the *shtadlanim*, the public representatives of the Jewish communities. They are too numerous to mention by name. Hasdai ibn Shaprut was one of the physician-statesmen. His letter to the King of the Khazars, who together with all his people embraced Judaism and established a Jewish kingdom in the eastern part of Russia, is still extant. Judah Abravanel was a physician and a statesman. He is better known as a doctor by his Latin name of Leo Hebraeus. The whole Abravanel family is illustrious for its statesmen, though they were not successful in mitigating the Spanish inquisition with its autos da fé or stemming the expulsion of 1492 by appeal to Ferdinand and Isabella. Rabbi Kalonymus of Venice was physician to the Doge.

The tradition of rabbi-physician and physician-scholar was rooted deeply in Jewish character and persisted through the seventeenth and eighteenth centuries long after similar types ceased among non-Jews. In days of suffering and poverty and among the ignorant and benighted the honorable hyphenate later became the Hassidic rabbi, the miracle worker, who knew no medicine and was not rich in learning. The Jewish community ever looked with affectionate regard, sometimes with awe, on the doctor, even though he was less exalted and not so deeply respected as the great rabbi. The doctor as communal leader continued into the nineteenth century, particularly in Eastern Europe, and he frequently played well the honorable role among his people.

Though the tradition persisted, and is not extinct even to this day, it weakened as the nineteenth century, with its spirit of tolerance and air of freedom, broke the shackles of ages. Medicine, too, was freed from the bane of metaphysics and the paralyzing influence of scholasticism. It became in large measure a scientific discipline and demanded of its devotees undeviating worship at its shrine. The need for learning the vast accumulated knowledge and of keeping abreast of progress literally forbade the doctor to pasture in other than scientific fields. The days of Erasmus, when the scholar could take all knowledge for his domain, had disappeared. The humanist doctor, that noble figure of yesteryear, vanished from the scene. Rabelais could translate the aphorisms of Hippocrates from Greek into Latin, write his immortal Pantagruel and Gargantua, and be a doctor

of medicine. Sir Thomas Browne was a good doctor and wrote *Religio Medici* and *Urn Burial*. Not so the modern physician. He was compelled to make a choice. Keats gave up medicine to become a great poet. Schnitzler and Chekhov forsook medicine for literature. S. Weir Mitchell was both a good doctor and a good writer and so was Oliver Wendell Holmes, but they are the exceptions.

The Jewish doctors, too, had to make their choice, and most of them did. They brought to medicine the same passionate devotion which their forebears brought to other learnings, and became great doctors. This is not the place to call the roll. It is long and honorable. Their very multitude and the many who became famous, gave rise to the idea that the Jew has a flair or special aptitude for medicine. The vast numbers of Jews who flock to medicine somehow fortify this view. Is there truth to this assertion? Obviously there are many reasons why men go into medicine. The same social, cultural, economic and personal drives which motivate the non-Jew also motivate the Jew. Exclusion from other fields no doubt played an important additional role with the Jews. To say that proportionately more Jews than non-Jews go into medicine and that the number who have attained high fame is out of proportion to their numbers is true, but it is somewhat of a nonsequitur to conclude therefrom that the Jew has a special genius for medicine.

It is doubtful whether anybody has a native genius for medicine. There are outstanding examples of men who literally stumbled into medicine and became famous. The great Claude Bernard did. A bent, an inclination, a character make-up, a social sense may and probably does play a part in the choice of medicine as an art or way of life or as a profession, but hardly as a science. There are good practising doctors who are not scientists and there are great medical scientists who are not good practitioners. Whatever qualities are necessary to make a scientist in other fields also enter into the making of a medical scientist. Certainly there is nothing racial or Jewish about the science of medicine. Only wicked people with evil hearts could give birth to the foolish notion that there is an Aryan medicine and a Jewish medicine. Only evil and perverted Nazi minds, with ulterior motives to serve, could proclaim the malignant view that a Jewish brain or a Jewish heart differs from non-Jewish brains and hearts. It has taken untold millennia or, rather innumerable eons, to lay down the structural brain pattern of modern man, and there is no evidence that it varies from group to group. A few thousand years can change cultural and social patterns; they cannot alter anatomical structure or physiologic function.

It may be stated with complete assurance that the vast majority of Jewish doctors differ in no way as physicians from non-Jewish doctors. The good or bad features in the one are paralleled in the other and they often cancel each other out. In this sense doctors do not differ much from persons in other professions or other walks of life. But there is, it seems, a certain cultural pattern derived perhaps from social mores and based on historical tradition which, though also found in non-Jews, characterizes proportionately a larger number of Jews who continue in that historic tradition. Time is fast erasing the patterns, but they are still recognizable.

The Jew admires learning almost to the point of adoration. The respect for the learned man, for the scholar as well as for scholarship, is deeply ingrained in Jewish tradition. Quite generally the rabbi was respected more for his learning than his piety or religious office; indeed he won the regard of his peers and fame among his people essentially through his scholarship. Awe of the rabbi or teacher was compared to awe of the Lord. The rabbi often took precedence over the father and always over the rich man or even the honored man of affairs. This traditional love of learning has been transmitted by parents to children from generation to generation, down to this day. Learning was often combined with various pursuits, even lowly occupation. The combination of doctor and scholar was indeed very honorable. Among others, too, medicine was a noble and honorable profession; among Jews the esteem knew no bounds.

Another characteristic of the Jew, which put its stamp on the doctor as well, has been a combination of intense individualism and a deep social sense. These two paradoxically opposing traits have moulded Jewish character and given rise to much misunderstanding. Strong individualism brooks no restraint, flaunts authority, and makes rebels of people. Up to a point it is healthy, beyond that it leads to anarchy. Sound individualism leads to creativeness and respect for the dignity of the individual. It is the basis of true democracy. But without social obligation there can be no healthy social organism. A deep social sensebridles the individual and provides that cement which is so necessary to the preservation of the group and to its perpetuation. Medicine, too, requires, indeed is based upon, strong individualism and a sense of social obligation. A sense of ethics and morals and of duty to society makes for good membership in a community; it is indispensable to the character of a good physician. To question authority and yet to respect it; to have individuality and to be aware of social obligations; to rebel against evil and to curb it; to have ethical ideals and to test them on the touchstone of reality; to maintain a critical attitude toward knowledge and to respect learning: these are the necessary ingredients for the formation of good character. They also go into the making of a good doctor. If ingrained by tradition they form a sound and enduring basis. Jewish tradition has ever fostered them. The Jew as physician was expected to have those qualities. However, be he Jew or non-Jew, the physician who possesses them is worthy of his calling.

THE USE OF GLASS FIBRE PAPER AS AN ABSORBENT IN THE TISSUE LABORATORY

(A PRELIMINARY REPORT)

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Since the cellblock technique of examining the cytologic detail of body fluids was first introduced, there have been repeated and constant efforts to improve upon the method. Various modifications have been proposed, all having as their aim the procurement of a better tissue section.

In recent years cellulose sponges of various types have been used to absorb the cellular elements of the fluid and these in turn have been fixed in formalin and put through the routine procedure of paraffin embedding and cutting.

The technicians in our laboratory found that it was not easy to obtain good ribbons since the cellulose sponge cut with some difficulty. Because of this, I became interested in the use of glass fibre paper as a substitute for the cellulose sponge, the former having been found by our biochemist (Henry Wishinsky, Ph.D.) to have absorbent qualities.

This material, which had been procured by him from the Naval Research Laboratory, is also known as fibrous glass and is described as "a soft, white material which feels like suede and is free from shot, slubs or other inclusions. Physically, the fibres are smooth, cylindrical rods, obviously different from common paper-making wood-pulp fibres. They have an average diameter of one ten-millionth of an inch (0.25 micron). Glass fibres are produced synthetically by either blowing or spinning a molten stream of glass or slag. Blowing results in a wool used extensively as thermal insulation, while spinning yields discrete threads or filaments. Wool may be separated into coarse and fine fibres and those which are small in cross section (less than one micron) but of moderate length (greater than $\frac{1}{64}$ inch) may be made into paper. Spun fibres can be made sufficiently fine for paper-making and no separation of the product is required." (1)

The fibrous glass has moderate tensile strength and does not crumble when handled. It absorbs fluids with facility and adsorbs material to its surface. Its use as a conveyer for sediments obtained by centrifuging various fluids will be described.

A disc of fibrous glass is cut out from the sheet so that it is large enough to cover the bottom of a 50 cc. centrifuge tube (Fig. 1). Having been placed in the bottom of the tube (Fig. 2), the fluid is poured in (Fig. 3), and after balancing, the tubes are placed in the centrifuge. Following centrifugation, the supernatant fluid is decanted. Without disturbing the disc and sediment at the bottom of the tube, 10 per cent formalin is added and the material allowed to undergo fixation. After fixation is complete, the disc is recovered by grasping it with a forceps and removing it from the tube. It is then placed, face up, on a piece of filter paper

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FIG. 1. The appearance of the sheet of glass fibre paper and the method of cutting out a disc are shown.



FIG. 2. Illustrates the method of placing the glass fibre disc in the bottom of the test tube.



FIG. 3. Illustrates the method of pouring the fluid into the test tube.



FIG. 4. Shows the centrifuged sediment on 2 glass fibre discs which are being wrapped in filter paper for safe keeping prior to being processed through the Technicon.



FIG. 5. The appearance of a microscopic section of the fluid encased in the glass fibre paper is illustrated as viewed under normal lighting conditions. The fibres of the glass fibre paper are practically invisible.

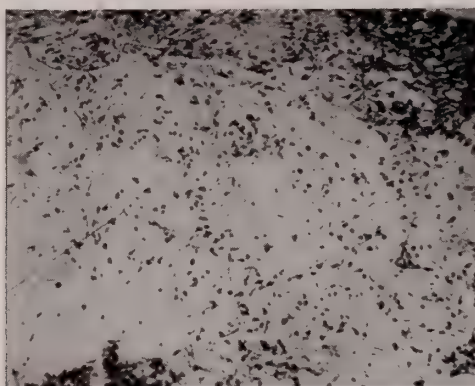


FIG. 6. Illustrates the appearance of the same slide shown in Fig. 5 when viewed under diminished light. Note the fibres of the glass paper have now become more prominent.

which is folded about it and acts as its carrier (Fig. 4). Processing then continues on the Autotechnicon through to its embedding in paraffin. In the "paraffin boat", it is placed face down, so that upon sectioning the most superficial sections will consist of material resting upon the surface of the fibrous glass disc, while the deeper sections will reveal the material absorbed into its meshes. If so desired the disc may be cut and embedded on edge. The material cuts with great ease on the microtome and ribbons are easily produced. In the case of fluids having a sparse cellular content the disc exhibits its greatest value, since the material obtained is encased within the meshes of the fibrous glass and can be sectioned in paraffin block, while without the use of the disc it would be insufficient for anything but a smear. Figure 5 shows the appearance of a section cut from the disc in which it is evident that the fibrous glass is, for all practical purposes, invisible and does not overshadow the cellular elements. Upon reducing the aperture of the diaphragm (Fig. 6), the diffraction produced increases the visibility of the fibrous glass, whose existence may otherwise be missed. The above described procedure is used in the case of fluids obtained from either the pleural or peritoneal cavities. When bronchial washings are submitted for examination, the material is transferred from the special aspiration tube to a small round-bottomed tube, either the usual Wasserman tube or something similar. A smaller sized disc of fibrous glass is placed in the bottom of the tube and the fluid then poured in. The procedure is thereafter similar to that described above. By this means, one is able to obtain cell blocks of even minute quantities of cellular material obtained by bronchial irrigation or suction.

The method described above has been in use in our Laboratory for the past two years. We have found it superior to the usual method of handling a "button" of sediment in a centrifuge tube, which almost invariably results in a crumbly mass which is conveyed through the dehydrating and embedding process in a folded piece of filter paper. By the glass fibre paper method very little material is lost and small quantities, which would otherwise be unavailable for cell block, are easily examined. Smears of the material centrifuged have been made in all cases and stained by the Papanicolaou technique. These have been studied in conjunction with the cell blocks and the two have been found to complement each other.

SUMMARY

The use of glass fibre paper is presented as an aid in the preparation of cell blocks of various body fluids.

The advantages of this method are noted.

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AN APPROACH TO AN ATHEROGENETIC FACTOR

TRANSINTIMAL PERFUSION

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As all students are influenced by the approach of their teachers, so have those pathologists fortunate enough to have studied under Dr. Paul Klemperer been guided into attitudes toward anatomical pathology. The training in critical observation with which Dr. Klemperer began the schooling of a pathologist was the framework for his development of interpretation and for his encouragement of exploration into the evolution of human abnormalities. Pre-eminent among the attitudes toward anatomical pathology at The Mount Sinai Hospital was that which emphasized that factual observation, "dead-house pathology", was not enough. The morphologic observations of a pathologist are of little value until they assume a dynamic structure which will serve to clarify the process from which the morphologic fact evolved. This can be accomplished only by familiarity with normal and abnormal physiology, chemistry, and physical information, and the use of the techniques of other disciplines in morphologic study. Structure without function is as meaningless as function without structure. As each scientific discipline contributes to the pool of information, so it enlarges all others. In this manner, morphologic study is an inexhaustible source from which biological dynamics may be explored. Dr. Klemperer's ever increasing application of the techniques derived from chemistry and physics to anatomical study and his wide interest in human and experimental physiology have been a stimulus to his students. He has illuminated the limitless possibilities for the use of the morphologic discipline.

This paper is derivative in all senses of the term. Many of the pathologic observations were made in Dr. Klemperer's laboratory. The successive interpretation, construction of a theoretical model, experimental evaluation, and verification by a return to human morphologic study is an attempt to follow the pattern of good scientific method which is the heritage of the students of Paul Klemperer.

This presentation will describe the approach to the study of a mechanism, which may play a significant role in the production of atheromata, based upon observations made at the autopsy table, and the design of the experimental procedures used to evaluate the procedures. The study is by no means complete, but enough data have been accumulated to reach some tentative conclusions and to form a basis for further exploration and discussion.

THE ANATOMICAL OBSERVATION

Over the past few years, we were fortunate enough to have available for study a series of cases in which the atheromatous processes appeared to be related to a

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disturbance of a factor which is essential in maintaining a normal state of tissue nutrition. This factor is that of TRANSINTIMAL PERFUSION, and the disturbance is a reduction of the transintimal perfusion of tissues. Specifically, these cases were instances of a pathologic block to the transfer of fluids and solutes from the blood stream into the tissues immediately underlying the intima of large vessels. In these malnourished tissues, free lipid aggregates appeared, increased in concentration as the block was maintained over a period of time. The pathologic block consisted of a thick, firm, fibrin thrombus deposited on the intimal surface of the aorta by some mechanism as yet unexplained. We have personally studied a number of cases of this entity as well as a number of other cases which may have had their inception as this lesion (1). We have reviewed cases kindly loaned to us by other pathologists which appear to fit the criteria established for this lesion. The criteria for this pathological entity are as follows:

(a) the aorta or other major artery must be morphologically normal, in the sense that the basic structure of the vessel is intact and there are no recognizable stigmata of primary vessel wall disease;

(b) a grossly visible massive thrombus must overlie the intimal surface of the vessel;

(c) the thrombus must be composed of a relatively acellular fibrin meshwork which may display varying degrees of degeneration and coagulation as the thrombus ages;

(d) reaction to the thrombotic mass usually arises first in that part of the vessel wall under the most peripheral parts of the mass, whence organization progresses for a short distance into the thrombotic mass.

It is not the purpose of this presentation to discuss this entity or to speculate upon its etiology. Rather, this experiment of nature offers the opportunity to study the changes which occur *beneath* the thrombotic mass.

The following correlation has been observed; as the thrombus persists, and rough estimations of the age of the thrombus are possible by evaluation of the degree of degeneration and extent of organization of the periphery of the mass, there appears, in the sub-intimal connective tissues of the vessel, immediately adjacent to the media, first, minute deposits of free fat, later followed by larger aggregates, and finally by lipid, lipophages, and cholesterol crystals. The lipoid appears in the deepest portion of the sub-intimal tissues and is separated from the overlying thrombus by a well-defined connective tissue which converts very slowly from the typical loosely-organized subintimal connective tissue to a condensed form of a hyalinoid character. The granulation tissue which tends to organize the thrombus arises lateral to the thrombotic mass and does not derive from the area under question.

THE INTERPRETATION

With this correlation, the question of the mechanism of the appearance of the lipid and its relationship to the overlying mass must come under scrutiny. It is difficult to implicate other factors in this localized atheromatous process because, first, the atheromatous lesions occurred only beneath the thrombi and at no

other place in the vessel wall, and, second, the patients had no other metabolic or cardiovascular abnormalities by both clinical observation and exhaustive pathological study. How, then, can the one lesion be related to the other? Clearly, since the younger thrombi have only infinitesimal lipid lesions beneath them, and the older thrombi have increasingly larger lipid aggregates, it is most likely that the thrombus preceded the appearance of the lipid. Since there is no physical connection between the thrombotic material and the lipid, the fatty material cannot have originated in the thrombus. This is contrary to the opinion of Duguid (2) and Rannie and Duguid (3) that atheromata may originate from lipid-containing macrophages deposited on the intimal surface. Furthermore, since the reaction of organization develops *lateral* to the edges of the thrombus and proceeds in a centripetal direction, whereas the lipids are located *centrally* beneath the mass, it is difficult to conclude that the appearance of the lipids represents an aspect of the organization process.

We are, therefore, led to the conclusion that the lipids arise from the connective tissues of the subintimal area because of physical changes induced by the overlying thrombus. Various metabolic mechanisms may be invoked to explain this origin of the lipid, for example (a) splitting of lipoprotein complexes of connective tissues to release free lipids, or (b) metaplastic transformation of the connective tissues to the lipid-containing form. The approach to this question is a dual one; first, by what means may such metabolic changes be induced, and, second, what morphological and physico-chemical changes of the connective tissues are associated with the appearance of these lipids.

The most obvious answer to the first question is suggested by the location of the lipid and its geographic relationship to the thrombus. That is, the thrombus may act as a dam to the perfusion of the inner portion of the vessel wall by fluids and solutes derived from the plasma within the vessel lumen. The existence of such a perfusate is suggested by two collateral observations: (a) Injection of a finely particulate dye into the small adventitial vessels of the vasa vasorum reveals vascular channels only so far as the junction of the outer two-thirds and the inner third of the media (4). Inspection of normal vessel walls reveals very few capillaries in the inner third of the media and none at all in the subintimal tissues. (b) The biological application of Poiseuille's Law concerning the characteristics of flow and pressure in tubes indicates that a significant degree of pressure is maintained laterally against the inner wall of a blood vessel. This is only partially accommodated by the stretching of the elastic wall. We can assume that a significant head of pressure is available to force a perfusate into the tissues of the vessel wall (5). This activity is similar to the capillary perfusion problem studied by Zweifach (6).

It is now possible to visualize a model of the wall of the aorta based upon the origin of the nutrition of its various layers. The intima and subintimal connective tissues are probably supplied mainly by perfusion from the intraluminal plasma. The adventitia and the media are nourished through the capillary branches of the vasa vasorum. The junction of these two systems, an end-artery locus in the nutritional sense, is the region of the internal elastic lamella.

Reduction in nutrition will produce morphological changes when the critical lower limiting value for homeostasis is passed. Reduction or complete loss of the perfusate appears to cause these changes. The reduction of the perfusate may be due to either reduction of the lateral pressure within the lumen or a mechanical block to perfusion in the presence of a normal lateral pressure. The latter mechanism is believed to be operative in the cases referred to above.

The appearance of free lipid may then be interpreted as the morphologic change which indicates a reduction in nutrition to the subintimal tissues. The appearance of free lipids in tissues affected by a local restriction of nutrition is a widely recognized biological phenomenon. Fatty metamorphosis or fat phanerosis in the kidneys, myocardium, and pancreas are phenomena which may be induced by anoxia or the reduction of other essential nutrients.

On the basis of observations made on human cases of lipid deposits appearing under mural aortic thrombosis on otherwise normal aortic walls, it is proposed that the appearance of free lipid in the subintimal connective tissues might be based on a reduction of the trans-intimal perfusion of fluids and solutes derived from the lumen, and that this reduction institutes a series of biophysical and biochemical changes resulting in the release of free lipids from their natural protein-bound state. In addition, the affected tissues are no longer able to utilize lipids delivered to them by way of the vasa vasorum. The end result is recognizable as atheromatous aggregates in the vessel wall.

THE TESTING OF THE HYPOTHESIS

It remains now to test this hypothesis. In our laboratory we have begun this study from two points of view: (a) further observations on vessels in which decreased perfusion might be expected by reason of a localized decrease in lateral pressure, and (b) animal experiment to duplicate blocks to perfusion. Of those vessels in whose lumina there is a decrease in lateral pressure, the only vessels found which partially meet the criteria of the model are the original aortic channels in cases of dissection of the aorta where the dissecting channel has ruptured back into the normal channel, the double-barrelled aorta. In these vessels, the cross-sectional area of the blood channel is increased, and the lateral pressure is decreased. Study of that portion of the aortic wall not involved in the dissection (opposite to the dissection) meets some of the criteria. Unfortunately, the damage to the aortic wall by the dissection is difficult to assess. Simple aneurysms are not suitable for such analysis because of the amount of preceding damage to the tissues of the vessel wall. Although the pressure characteristics in congenital coarctation are not entirely clear, it is possible that the aortic segment immediately distal to the narrowing may meet the criteria of normal wall and decreased lateral pressure.

The animal experiments have been directed toward the production of artificial blocks to perfusion while maintaining the integrity of the vessel wall. The results have been encouraging. By pleating a portion of the aortic wall of an animal, taking precautions not to damage the perivascular connective tissue carrying the vasa vasorum, the perfusion of the pleated portion of the wall is reduced to a

minimum. In half of the guinea pigs who survived this procedure, lipid appeared in the pleated portion of the vessel, and no lipid was found elsewhere. The experiment was repeated with rabbits, and one-third of the surviving animals showed increase in lipid (7). The technical difficulties and attendant hemodynamic side-effects makes this procedure of questionable value.

Recently, a procedure has been devised which permits the insertion of a plastic tube, the outside diameter of which is approximately the same as the inner diameter of the aortic lumen, into the aorta, without damage to the portion of the wall of the vessel under observation (8). This produces an artificial block similar to the thrombus of the human cases. This method is still under study for its general hemodynamic effects before evaluation of the induced structural changes is undertaken.

TRANSINTIMAL PERFUSION IN COMMON ATHEROSCLEROSIS

This study would be of little value if it did not apply to the common atheromatous process. In such cases there is no intraluminal block to be found. It was suggested that the subintimal tissues themselves may be so transformed by the aging of connective tissues to reduce the perfusion necessary for homeostasis in the depths of the vessel wall (9). This would correspond to the thickening and hyalinoid material found replacing the fibrillar subintimal tissues in aged individuals, the changes currently being studied from the point of view of mucoprotein alterations. It is necessary, therefore, to extend our previously described studies to include a re-examination of the characteristics of the vessel wall which permit of perfusion.

This approach is not meant to minimize all of the other factors which play a part in the pathogenesis of atheromata such as hypercholesterolemia (10), lipoprotein particle size (11), association with the multiple metabolic abnormalities of diabetes mellitus (12), the hydrodynamic abnormalities of systemic hypertension (13), or many others (14). It is rather suggested that the total osmotic activity must depend as much upon the nature of the membrane to be crossed as upon the chemical and physical characteristics of the fluid.

Our knowledge of the physical properties of the wall of the aorta is incomplete. Studies have been initiated to resolve a number of questions. The principle problem is to determine the degree of perfusability of the aortic wall under the lateral pressure head commonly found in that vessel. Direct measurement in humans is not feasible at present. A method for indirect measurement has been developed by which the degree of penetration of a dye of small molecular size into the wall may be evaluated. Simultaneously, measurements of the tensile strength and the capacity of the aortic wall to stretch have been undertaken in the belief that such measurements will show a correlation with the penetration experiment and may be used as an index to the character of the membrane. (15) It became quite clear, early in these examinations, that the total membrane activity of the aortic wall is a complex phenomenon resting on the individual membrane activity of the three major aortic layers, the intima-subintima, the internal elastic lamella, and the media-adventitia. The studies have been ex-

tended to include measurements on these three layers, individually, after microdissection of selected fresh specimens, in an effort to arrive at a baseline for the physical characteristics of the aortic wall and its parts during the ageing process and the variations associated with demonstrable aortic disease.

It is hoped that these studies will yield information about the membrane through which the plasma perfusate must pass. If the physical characteristics of this membrane change significantly with age, as has been indicated by many studies (16), that is, if the subintimal connective tissues condense into a non-perfuseable tissue, it may be concluded that an internal dam to perfusion has been established. The effects of this block may be compared with the intraluminal dam observed in pathologic material and produced by animal experiment. The relation of lipidization of a vessel wall to the factors governing the perfusion of the wall may then be determined.

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SELF-HEALING HYPERNEPHROMAS

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While studying the phenomenon of spontaneous regression in epidermal cancer (1), our attention was drawn to Hultquist's findings (2, 3) on self-healing hypernephromas. The present report is based on autopsy material collected from a small hospital over a two year period and emphasizes the common occurrence of spontaneous regression of cortical renal cancers, particularly of the clear-cell variety.

CASE I

T.A. (Adm. No. 20), a woman of 86 with a history of hypertension, was admitted with right hemiparesis, and sensory aphasia. She died six weeks later. Au-

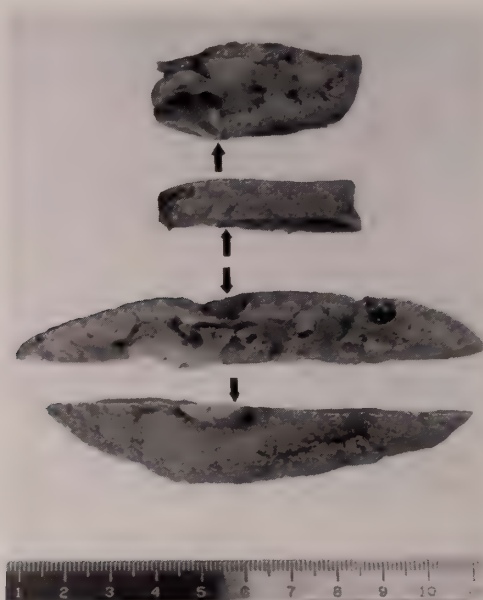


FIG. 1. Case I. Bilateral renal tumors. The two upper segments show cut surface and subcapsular surface of hypernephroma (Tumor 1). The two lower segments show the same view of a tubular "adenoma" (Tumor 2) which occupies the bottom of a crater-like pit.

topsy (A4-54) disclosed a great variety of findings, notable among which were healed, rheumatic carditis, obsolete, pulmonary Ghon tubercles and calcified, intramuscular trichinella larvae. She had a right radical mastectomy fifteen years before which, seemingly, was curative. (We were not able to get more detailed information on that point.) The pertinent findings in the kidneys are shown in Figures 1-3 and discussed in the legends.

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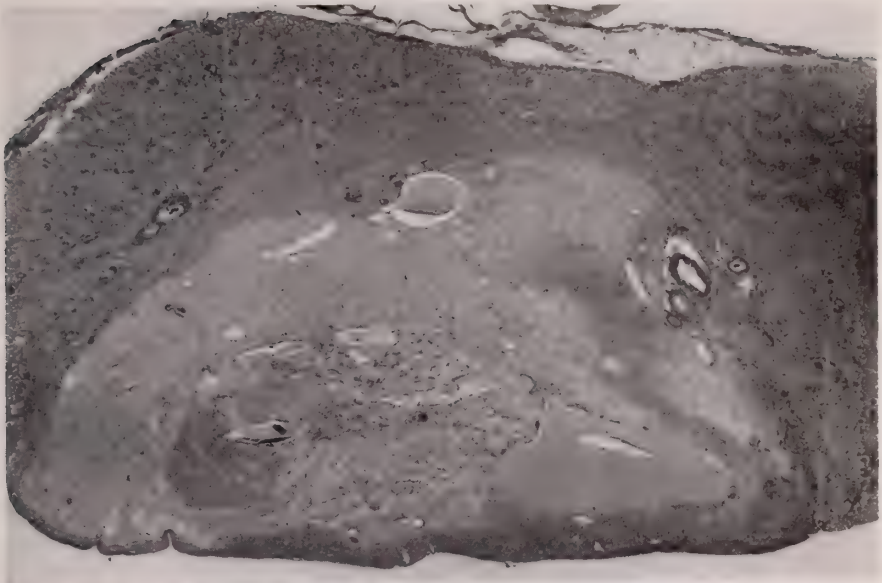


FIG. 2. Entire cross sectional view of Tumor 1 corresponding to top segment of previous figure. The bulk of the lesion is composed of edematous and cystic fibrous tissue.

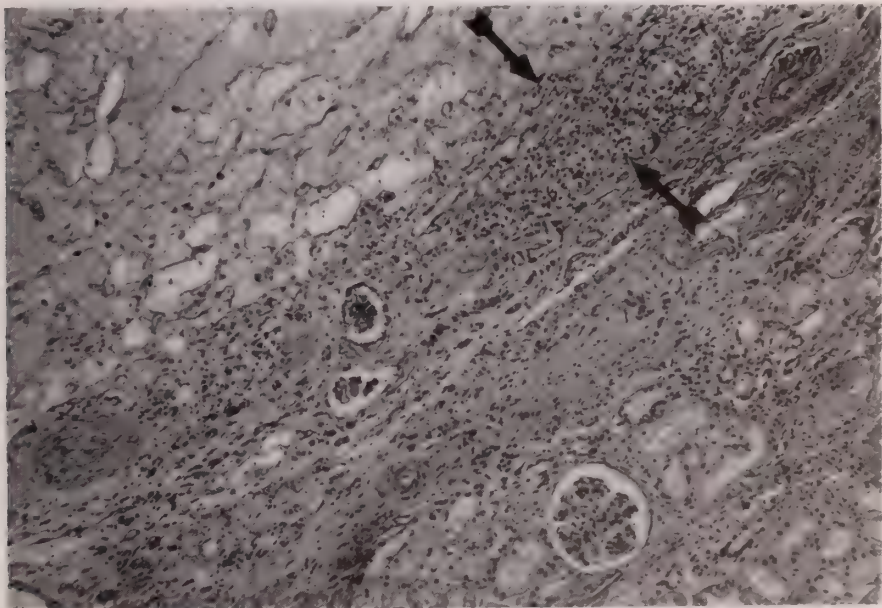


FIG. 3. Margin of Tumor 1 with rim of viable clear-cell cancer between arrows.

CASE II

R.B. (Adm. No. 12694), a woman 71 years old, was admitted for cardiac failure and coma accompanied by uremia to which she succumbed in a few days. Post mortem studies (A 55-55), disclosed among other findings severe calcific mitral stenosis and the renal lesions depicted in figures 4 and 5.



FIG. 4. Case II. Bisected partly cystic cortical lesion (Tumor 3).

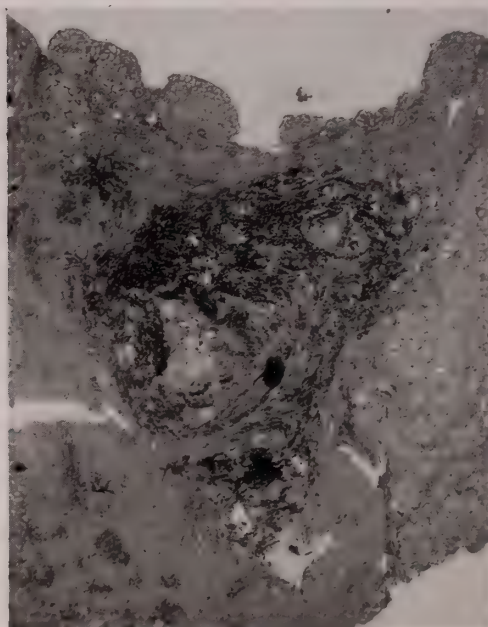


FIG. 5. Corresponds to lower segment of Figure 4. Abundant elastic tissue (Weigert's Elastica stain).



FIG. 6. Case III. Anterior view of horseshoe kidney. Arrow on left points to Tumor 4, arrow on right to Tumor 5 which is attached to peeled off capsule. Central arrow shows surface pit caused by Tumor 5. Right half of Figure 6 gives close up of cut surface of calcified Tumor 4.

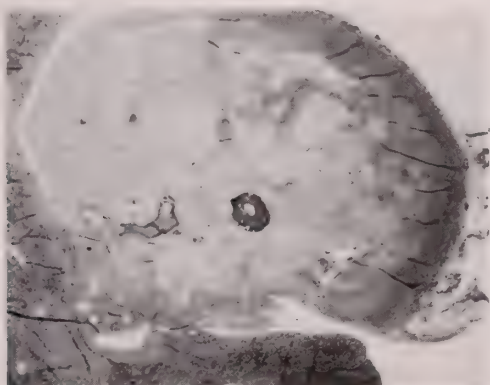


FIG. 7. Complete cross section of Tumor 4 with calcified vessels. At this level the tumor is totally fibrotic.

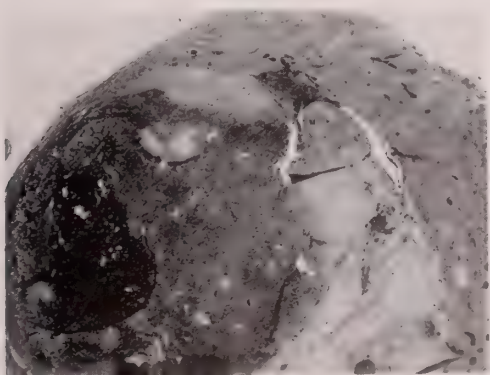


FIG. 8. At another level Tumor 4 shows viable hypernephroma with fresh hemorrhage. The findings of tumor 5 were essentially similar.

CASE III

R.S. (Adm. No. 19277), a man aged 62 with a history of hypertension and episodes of cardiac failure and "small strokes", was hospitalized for coma and right hemiparesis. Death came on the third day. Necropsy (A 68-55) showed in addition to the anticipated findings in brain and heart a number of other ones of which the horseshoe kidney with its two subcapsular tumors is of main interest (Figures 6-8).

DISCUSSION

Various microscopic regressive features are frequently seen in the common small subcapsular papillary cystadenomas, while the typical large hypernephroma almost always discloses a number of necrobiotic and reparative phenomena which account for its variegated cut surface. Hultquist (2, 3) apparently was the first to emphasize that certain cortical renal scars are caused by regressing or obsolete hypernephromas. Metastases from hypernephroma may be few or solitary or disappear spontaneously, i.e., that there is a certain inherent frailty to this type of tumor. The present report although based on much smaller material and lacking serial section studies confirms the common occurrence of these lesions. The majority of Hultquist's tumors appeared as a depressed surface scar from the bottom of which arose a papillomatous structure caused by the wrinkled capsule of the shriveled tumor. Most of our lesions were either less contracted or smaller and thus failed to show this corrugated appearance. The possibility of tuberculosis or endocrine disturbances as important factors in the regression of hypernephromas is mentioned by Hultquist; our own series is too small for studies of this kind.

SUMMARY

Partial or complete healing of small cortical renal tumors, particularly of the clear-cell variety is a common finding. These lesions may impress as banal scars. Five tumors, some of which were multiple are reported.

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IN EXPLANATION OF CERTAIN GLIOMA PROBLEMS

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Numerically the most important human intracranial neoplasms are the gliomas which, it is variously estimated, constitute about 50 per cent of all primary tumors in this location. In spite of the fact that they have received serious study since 1926 when Bailey and Cushing (1) first proposed a classification for them, many problems regarding them are as yet unanswered. There is, for example, the question of their histogenesis. Also, the reason is obscure why certain gliomas occur frequently in some parts of the brain and rarely in other. A third problem is the known fact that gliomas, even the most malignant, fail to metastasize spontaneously extra-cranially. Finally, there are the problems which are concerned with environmental influences, including x-radiation, on the morphology and biologic behavior of this group of tumors.

Experiments designed to supply answers to some of these questions have engaged the attention of the present writer and his associates at various times since 1940. The results of some experiments published in 1941 (2), in which pure methylcholanthrene was utilized in the form of minute, compressed pellets for implantation into different regions of the brains of several inbred strains of mice, proved that this chemical carcinogen could be used as a tool in procuring answers to some of these questions (Fig. 1). In 1943 it was shown that both benzpyrene (3) and dibenzanthracene (4) were also effective in inducing gliogenous neoplasms in mice. The applicability of the experimental results to the problems of human gliomas was shown in a paper published in 1955 (5).

THE HISTOGENESIS

It is generally accepted that all adult glial cells and neurons are derived from a single embryonic cell type, the medullary epithelium. These various cells reach adulthood by a process of differentiation. In this process the astrocyte, as an example, presumably passes through stages in which the bipolar and unipolar spongioblast and the astroblast represent its forefathers in a direct line of descent. To account for the presence of anaplastic cells; i.e., spongioblasts and astroblasts, in a rapidly growing glioma, the concept of dedifferentiation has been elaborated. As part of this concept there is the assumption that in the formation of a glioma a single adult glial cell is somehow stimulated to proliferation, and that the full-blown neoplasm thus has its origin from but a single cell.

The cellular pleomorphism which may be present in any glioma is attributed to dedifferentiation; but does this explain the several different types of cells which frequently are found in such a tumor? Does this concept adequately account for the presence of astrocytes in an ependymoma or oligodendroglioma? Or is there

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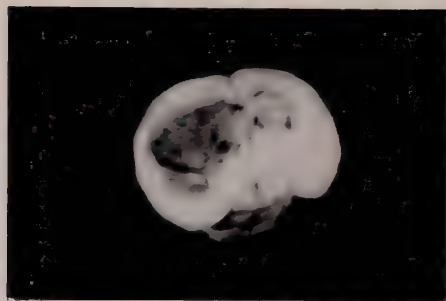


FIG. 1. Appearance of ependymoma which has arisen in lateral ventricle at site of an implanted pellet of methylnholanthrene.

a better explanation for the frequent coincidence of tumor cells of different types in a glioma?

The experiments with chemical carcinogens already mentioned clearly showed that few of the cerebral neoplasms were composed of single cell types, that is, were "pure" tumors. Most of them were tumors composed of several different cell types and hence constituted "mixed" tumors. Microscopic study of the origin of the carcinogen-induced experimental brain tumors revealed the fact that the chemical injured a number of different glial cells. This injury was apparent from the pigment deposition within cells which bordered on the implanted carcinogenic pellet. In due time evidence of cellular proliferative changes appeared affecting a variety of cell types. In other words, the almost simultaneous proliferation of *several* adjacent glial cells occurred to produce the gliomas. Since these tumors were derived from several *different* progenitors, they were not "pure" gliomas. As they continued to grow, different parts of them presented diversified cellular populations, depending on the number and kind of glial elements which had been stimulated to neoplastic activity by the carcinogen. Another factor which determined the appearance of the tumor was the rate of growth of the different cells present. The more rapidly growing spongioblasts, for example, in time overgrew and replaced the more slowly proliferating astrocytes.

In this view of the histogenesis of experimental gliomas, the concept of dedifferentiation has a distinctly limited role. It can account for astroblasts and spongioblasts in a tumor derived from adult astrocytes, but it does not explain the presence of oligodendroglia and ependymal cells in a slowly growing astrocytoma.

Additional evidence in support of the "mixed" nature of the gliomas is afforded by transplantation experiments in which the primary intracerebral tumors were sectioned into minute fragments for subcutaneous transplantation (Fig. 2). With such tumor transplants it has often been possible to establish two or more sublines of "pure" gliomas. Once established subcutaneously, the "pure" tumors could be subtransplanted indefinitely through generation after generation, always remaining morphologically constant. This experimental evidence suggests that gliomas are multipotential, one "mixed" tumor being capable



FIG. 2. Subcutaneous transplant of a malignant glioma. The skin of the flank and abdomen has been dissected away to reveal the large, non invasive neoplasm. The transplant (diameter 2 mm.) grew to the size in the photograph in 32 days.

of yielding several "pure" tumors by judicious and/or fortunate transplantation. This, of course, corresponds to the results achieved by the microbiologist who succeeds in obtaining several pure bacterial strains by selecting suitable colonies from a mixed culture. The multipotentiality of the gliomas has a counterpart in another class of tumors; namely, the lymphomas. The latter, also, may assume many guises: different lymph nodes at different times in the same individual may have divergent morphologic appearances.

SITES OF PREDILECTION

The implantation experiments with pellets of carcinogen in the brains of animals disclosed interesting facts which bear on the question of the sites of predilection of this class of human tumors. It was demonstrated that the type of glioma produced by this means varied with the location in the brain where the pellet was placed. When in contact with the ventricular ependyma, the carcinogen induced the development of an ependymoma or ependymoblastoma. In the occipital lobe subcortex, it frequently was responsible for an oligodendroglioma; the same tumor was also seen in the frontal lobes. In the corpus callosum it induced a spongioblastoma polare; in the cerebellum, a medulloblastoma. The

most frequently encountered experimental glioma was the glioblastoma multiforme, and its favorite site was the central white matter of the parietal lobes. This, however, was also the usual site of the occasional astrocytoma.

These are also, in general, the sites of predilection of the human gliogenous neoplasms (6). The coincidence of the human and the experimentally induced tumors appears strange and is perhaps more than fortuitous. But as yet there is no valid explanation for the tumor predilections.

EXTRACRANIAL METASTASIS

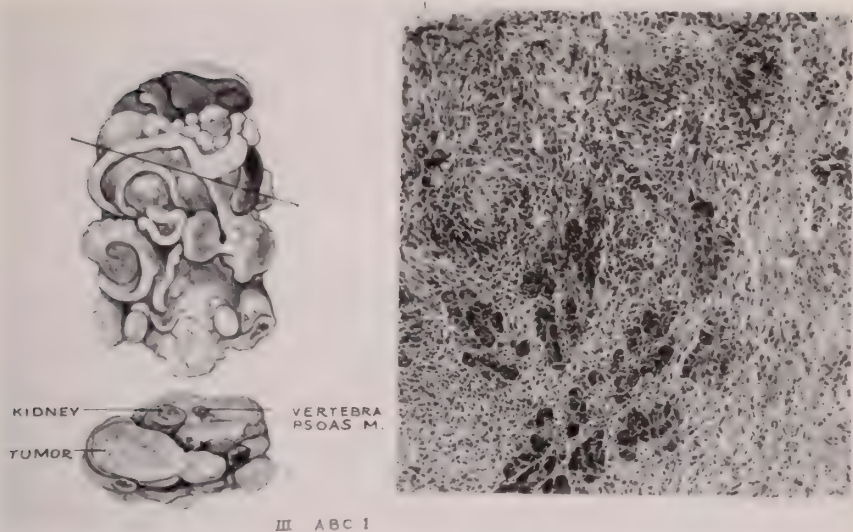
It has long been recognized that the more malignant gliomas like the medulloblastomas, ependymomas and glioblastomas multiforme are capable of spreading along the cerebrospinal fluid pathways. Extracranial metastases from these and other gliomas are practically unknown. In the few instances where such metastases were seen, prior surgical intervention for operative removal of the neoplasms suggested possible routes of metastasis by way of the blood stream.

The obvious explanation for the absence of distant metastases from intracranial gliomas is that there is no readily accessible pathway for the spread of these tumors. Aside from the lack of a lymph vascular system in the brain and spinal cord which could serve as a route for extracranial spread of these tumors, their inability to invade blood vessels is notorious. This is true for both the human and the experimental neoplasms. Tumor thrombi, for example, are never seen in gliomas, even in their most malignant form such as the glioblastoma multiforme, a neoplasm often characterized by spontaneous hemorrhage, endothelial proliferation and thrombosis. Neoplastic cells are almost never found invading blood vessel walls.

Gliogenous neoplasms, however, will grow extracranially quite readily when provided with mechanical transportation. This must already be clear from the references to the subcutaneous tumor transplantation experiments. Some years ago, Freeman and I (7) also reported successful intraocular transplantation in both homologous and heterologous strains of mice. Through accident and by design it has been repeatedly demonstrated that experimental gliomas grow equally well in the pleural and peritoneal cavities. Finally, it has also been possible to produce widespread visceral metastases in mice by the intravenous injection of tumor homogenates (Fig. 3). In mice as in man, gliomas do not metastasize spontaneously extracranially.

MORPHOLOGY AND BIOLOGIC BEHAVIOR OF GLIOMAS AS INFLUENCED BY ENVIRONMENT

In the study of neoplasia in general, no less than of gliomas, emphasis is almost always placed on the tumor rather than on the host. Expressions such as "autonomy" and "autonomous growth" are symptomatic of this emphasis and imply complete independence of behavior on the part of tumor cells, uninfluenced by external forces such as the patient's tissues, immune reactions and other environmental considerations. That the environment in which the tumor finds itself does influence its appearance and behavior will perhaps become apparent



III ABC 1

FIG. 3. Drawing of retroperitoneal and intraabdominal tumor (glioma) metastases which resulted from injection of homogenate into tail vein of mouse. Photomicrograph discloses infiltrating cells of malignant glioma among acini of pancreas. Hematoxylin-eosin stain.

from the following. These considerations may explain the remarkable variations which are often noted in tumors of the same classification.

The growth behavior of chemically induced mouse brain tumors were studied by Cohn and me in the chick embryo (8). Utilizing both an ependymoblastoma and a mixed, malignant glioma which had been carried through many generations of subcutaneous transplants, striking differences were shown in the growth behavior of these neoplasms when grown on the chorio-allantoic membranes of hen's eggs. The characteristic microscopic appearance of each of these neoplasms was lost in the egg. Tumor cells grew in loose clusters and invaded the mesenchyme of the chick embryo. The ependymoblastoma, for example, lost its ability to produce pseudorosettes except on rare occasions. When the egg-grown tumor, however, was transplanted back into the mouse, it invariably regained its distinctive original pattern. This happened regardless of the particular appearance of the tumor in the egg and regardless of the number of egg passages through which the tumor was carried. These experiments show clearly the effect of environment on tumor morphology.

An environmental influence which may alter growth behavior of gliomas was demonstrated in experiments on the effects of single roentgen radiation doses on this class of tumors (9). Dosage levels up to 5000 r created striking morphologic changes in the experimental tumors grown in subcutaneous transplants. Multinucleated tumor giant cells appeared in large numbers and such characteristic structures of certain gliomas as rosettes completely disappeared. With intermediate doses there were transient depressions of tumor growth. With high dose levels, the tumors were either completely destroyed or showed "di-phasic growth", by which is meant regrowth of the tumor after an initial in-

hibition in its size. Some tumors appeared to melt away, only to display extraordinarily rapid growth later. The size of such gliomas at a stated time following therapy often matched that of the control neoplasms, which meant that the irradiated tumor cells grew more rapidly than the non-irradiated cells. Stated another way, inadequate or incomplete roentgen radiation had the effect of stimulating growth of these experimental gliomas.

SUMMARY

Experiments are described which contribute to an understanding of: 1, the histogenesis of gliomas; 2, the preferential localization of gliomas in certain regions of the brain; 3, the lack of extracranial metastases of this class of neoplasms; 4, some environmental factors which influence their morphologic characteristics and growth behavior.

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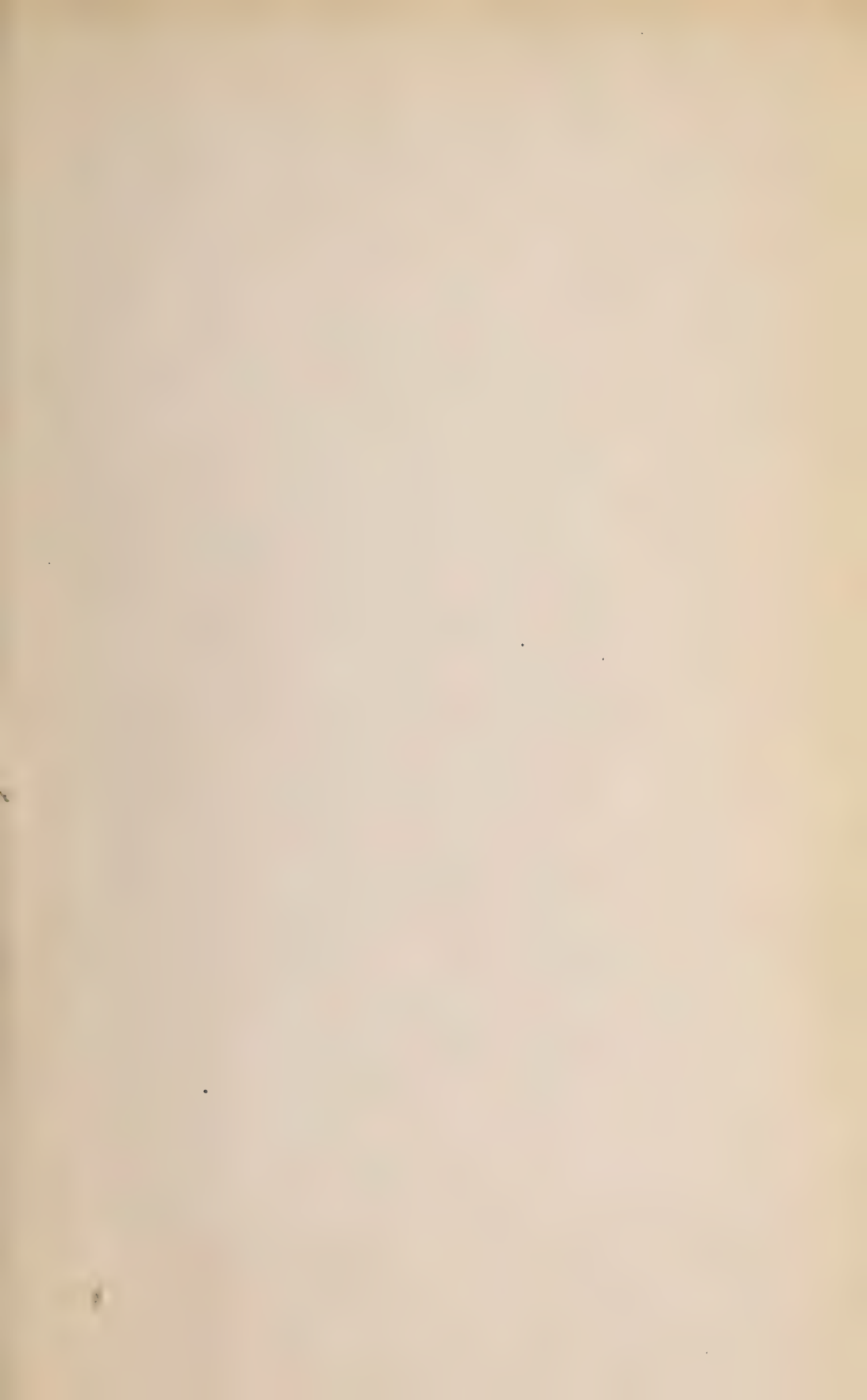
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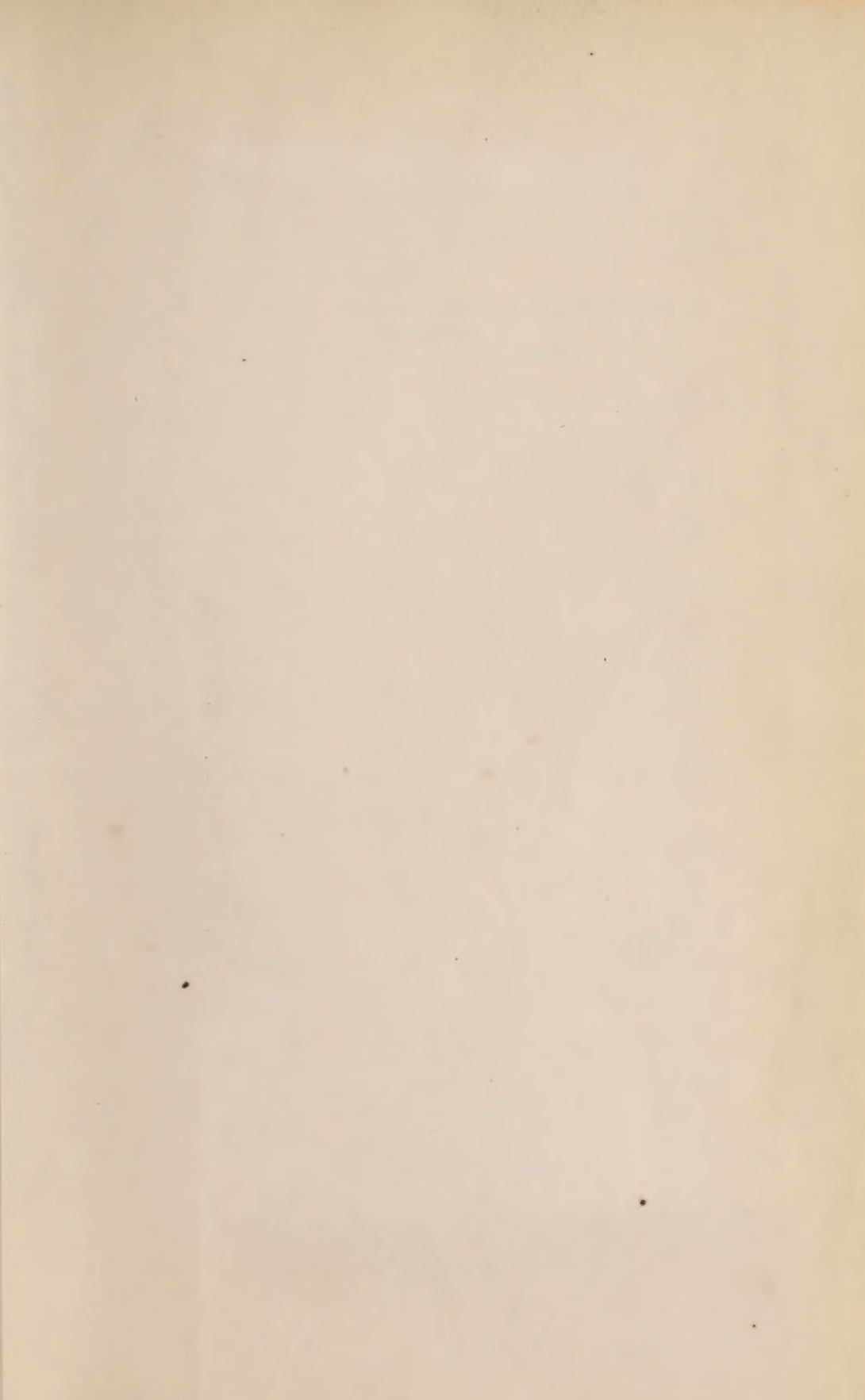
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